MEDICAL PROCEEDINGS

MEDIESE BYDRAES

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REDAKSIONEEL · EDITORIAL

DIE ROOK VAN SIGARETTE EN LONGKANKER

'N STATISTIESE LOKVAL

CIGARETTE SMOKING AND LUNG CANCER

A STATISTICAL SNARE

'Perhaps in the long run it will appear that the chief usefulness of the statistical technique in methodology of science is the not unimportant one of suggesting problems and lines of attack upon problems which must finally be solved, if they ever are solved, by the application of the methods of experiment and observation . . .'— Raymond Pearl in *Science*, 23 August 1929.

Die bewering wat aanhoudend herhaal word, nl. dat die rook van sigarette die belangrikste oorsaak van longkanker is, het baie mense onder die indruk gebring dat dié bewering gestaaf en trouens onweerlegbaar is. Inderdaad, in die Verenigde Koninkryk was hierdie geloof die basis van die beroep wat op 40,000 mediese praktisyns gedoen is om deel te neem aan 'n veldtog teen hierdie openbare euwel.[1] Die huidige toestand herinner 'n mens sterk aan die godsdiensywer wat 'n kruistog kenmerk.

Die voorstanders van die mening dat die rook van sigarette karsinogenies is (ten minste vir sover dit die longe betref) is merkwaardig houtgerus oor die feit dat die hele grondslag van hul geloof suiwer statisties is. Die basiese gegewens wat deur Doll en Hill[2] versamel is, het die bal aan die rol gesit, maar die steeds toenemende krag van onbevooroordeelde gegewens is geleidelik besig om die aansprake van diegene wat met 'n hartsorg vir wêreldhervorming besiel is, te ontsenu.

Een van die belangrikste bydraes tot 'n rasionele vasstelling van die posisie word

1. *Lung Cancer and Tobacco* (1956): Brit. Med. J., **1**, 1157, 1160.
   The Star, Johannesburg, 18 Mei 1956.
2. Doll, R. en Hill, A. B. (1952): Brit. Med. J., **2**, 1271.

The constantly re-iterated claim that cigarette smoking is the most important cause of lung cancer has persuaded many that the allegation has been proved and is inconstestable. Indeed, in the United Kingdom this belief has become the basis for enjoining upon 40,000 medical practitioners the duty of participating in a campaign against a public evil.[1] The situation smacks of the religiosity of a crusade.

The protagonists of the view that cigarette smoking is carcinogenic (at least as far as the lungs are concerned) are remarkably unperturbed by the fact that the entire foundation for their belief is statistical. The basic data accumulated by Doll and Hill[2] started the hare, but the gradually accumulating force of unbiased assessment is steadily and surely demolishing the claims made by enthusiasts with a passion for reforming the world.

One of the most important contributions to a rational evaluation of the situation is provided by Berkson's penetrating analysis of the problem, published elsewhere in this issue by permission of the Section on Publications of the Mayo Clinic. Dr. Berkson is a biometrician

1. *Lung Cancer and Tobacco* (1956): Brit. Med. J., **1**, 1157, 1160.
   The Star, Johannesburg, 18 May 1956.
2. Doll, R. and Hill, A. B. (1952): Brit. Med. J., **2**, 1271.

gedoen in Berkson se insiggewende ontleding van die probleem, wat elders in hierdie uitgawe gepubliseer word met die welwillende verlof van die Publikasie-afdeling van die Mayo-kliniek. Dr. Berkson is 'n biometris en 'n mediese statistikus, en die veelvuldige vergissinge in die redeneertrant wat die bourgeoissigaret geïnkrimineer maar die plebejiese pyp en die aristokratiese sigaar vrygeskel het, word deur sy kragtige argumente aan die kaak gestel. Hy bevind dat belangrike dele van die saak waarop die argument gebaseer is

'*prima facie* bewys dat hulle onderwerp is aan 'n soort seleksie wat assosiasie in die bestudeerde gegewens tot gevolg kan hê . . . selfs al bestaan die assosiasie nie by die primêre referensie-bevolking nie.'

Hy is ook nie geïmponeer nie deur die feit

'dat die aansienlike aantal statistiese studies wat gepubliseer is, almal 'n assosiasie tussen rook en longkanker aantoon. Inteendeel, die nie-afwykende konsekwentheid van statistiese resultate wat almal dieselfde gevolgtrekking steun, is in sommige omstandighede die waarmerk van onegte statistiese korrelasie. Indien die korrelasie geproduseer word deur sommige elemente van die statistiese prosedure self, is dit byna onvermydelik dat die korrelasie sal verskyn wanneer ook al die statistiese prosedure toegepas word.'

Dit behoort alledaags te wees (maar skynbaar is dit nie) om te sê dat dinge wat toevallig verbind is 'n hoë mate van statistiese korrelasie sal toon, maar dat 'n hoë mate van korrelasie tussen twee dinge wat bestudeer word, nie noodwendig 'n toevallige verband tussen hulle weerspieël nie. Ochsner se verslag[3] oor wat Evarts Graham in 1951 aan hom gesê is, is in hierdie verband van pertinente belang:

'Ja, daar is 'n parallelisme tussen die verhoogde voorkoms van bronchiogeniese karsinoom en die verkoop van sigarette; maar daar is ook 'n parallelisme tussen die vermeerderde voorkoms van bronchiogeniese karsinoom en die verkoop van nylonkouse.'

Rigdon en Kirchoff[4] word deur die kanker-en-rook-situasie herinner aan 'n spotprent wat onlangs in die *Saturday Evening Post* verskyn en die volgende onderskrif gehad het:

'Die buro kan nie verduidelik waarom die 4-persent-vermeerdering in die aantal huwelike in Arkansas in 1951 vergesel gegaan het van 'n dergelike vermeerdering in die verkoop van haelgeweerpatrone nie.'

'n Hoë mate van statistiese korrelasie toon bloot *prima facie* aan dat verdere ondersoek ingestel behoort te word, want statistieke het beperkinge wat nie oorskry kan word deur Procrustes-middele om antwoorde te vind wat

3. Ochsner, A. (1951): Harlem Hosp. Bull., **4**, 39 [Aangehaal deur (4)].
4. Rigdon, R. H. en Kirchoff, H. (1953): Texas Rep. Biol. Med., **11**, 715.

and a medical statistician, and his cogent arguments expose the multitudinous errors that infest the chain of reasoning which has incriminated the bourgeois cigarette, whilst exonerating the plebeian pipe and the aristocratic cigar. He finds that important parts of the case on which the argument is based exhibit

'*prima facie* evidence that they have been subjected to a kind of selection which can produce association in the data studied . . . even if the association does not exist in the primary reference population'.

Nor is he impressed by the fact that

'the considerable number of statistical studies published all agree in showing an association between smoking and cancer of the lungs. On the contrary, undeviating consistency of statistical results all in support of the same conclusion is in some circumstances the hallmark of spurious statistical correlation. If correlation is produced by some elements of the statistical procedure itself, it is almost inevitable that the correlation will appear whenever the statistical procedure is used'.

It should be (but apparently it is not) trite to say that things which are causally connected will show a high degree of correlation statistically, but that a high degree of correlation between two things studied does not necessarily reflect a causal relationship between them. Ochsner's report[3] of what Evarts Graham said to him in 1951 is very pertinent in this connexion:

'Yes, there is a parallelism between the increased incidence of bronchiogenic carcinoma and the sale of cigarettes; but also there is a parallelism between the increased incidence of bronchiogenic carcinoma and the sale of nylon stockings'.

Rigdon and Kirchoff[4] are reminded by the cancer-and-smoking situation of a recent cartoon in the *Saturday Evening Post* which stated:

'The bureau is unable to tell us how come the 4 per cent increase in marriages in Arkansas in 1951 is also matched by the increase in the sale of shotgun shells'.

A high degree of statistical correlation merely make out a *prima facie* case for further investigation, for statistics have limitations which cannot be transgressed by Procrustean devices to yield answers which only other methods of investigation can supply. These limitations are well borne out by another illuminating example from Dr. Berkson's paper:

'If . . . there is a positive correlation between stature and weight, then it is a descriptive fact that tall individuals in that population are on the average heavier than short individuals. But there is no concluding even here that there is a necessary

3. Ochsner, A. (1951): Harlem Hosp. Bull., **4**, 39 [Quoted by (4)].
4. Rigdon, R. H. and Kirchoff, H. (1953): Texas Rep. Biol. Med., **11**, 715.

slegs deur ander ondersoekmetodes opgelewer kan word nie. Hierdie beperkinge word pragtig toegelig deur 'n verdere insiggewende aanhaling uit dr. Berkson se referaat:

‚Indien . . . daar 'n positiewe korrelasie tussen lengte en gewig is, dan is dit die beskrywende feit dat lang mense in die bevolking oor die algemeen swaarder as kort mense is. Maar selfs hier kan daar nie tot die gevolgtrekking geraak word dat daar 'n noodwendige biologiese verband tussen lengte en gewig is nie; ons weet, byvoorbeeld, nie of die korrelasie nog sal bestaan as die bevolking op 'n heeltemal ander dieet geplaas word nie.'

In hierdie sake kan ons nie die plig ontwyk om te bewys dat daar 'n oorsaak-en-gevolgverband is nie. In die geval van rook en longkanker is dit beslis nie gedoen nie.

In die huidige geskil kan die saak wat deur die statistikusse gestel is, alleen deur biologiese eksperimente getoets word. Dit is klaarblyklik 'n baie ingewikkelde taak, die moeilikhede waarvan egter nie die voorbarige akrobatiese sprong tot die etiologiese gevolgtrekkinge waarop ons vergas is, regverdig nie.

'n Aktiewe opvoedkundige veldtog om teen die rook van sigarette te waarsku (soos Berkson heeltemal tereg aandui) staan skynbaar nie op vaste pote nie wanneer 'n ondersoek van die gegewens aan die lig bring dat die sterftesyfer ten gevolge van kanker onder sigaretrokers gelyk staan aan, of laer is as die ooreenstemmende syfer onder die algemene publiek, en dat die globale sterftesyfer van eersgenoemde groep ook laer is.[5]

Die saak teen 'n toevallige verband tussen die rook van sigarette en longkanker berus op veel meer as misleidende statistiese assosiasies. Die ondersoek is ook verdag weens die heeltemal subjektiewe aard van die gegewens in verband met die hoeveelheid tabak wat gerook word.

Die buitengewone feilbaarheid van die mens se geheue vir navorsingsdoeleindes word toegelig deur die menslike maandstondsiklus. Die meeste vrouens is oortuig daarvan dat hulle die begin van hul maandstonde met akkuraatheid kan voorspel. Hierdie aanspraak is nie verrassend nie, want dit is 'n opvallende verskynsel waaraan daar soveel sosiale ongerief verbonde is dat 'n mens by die eerste oogopslag geneig sou wees om te sê dat dit iets is wat 'n vrou nie sommer maklik sal vergeet nie. Maar as sy boek hou, ‚ontdek sy baie gou dat haar maandstonde nie verskyn met die presiesheid wat sy verwag het nie.'[6] Hierdie feit is deur uitgebreide navrae so deeglik bevestig dat dit

5. Berkson, J. (1956): Proc. Staff Meet. Mayo Clin., **10,** 338-339.
6. Hartman, C. G. (1936): *Time of Ovulation in Women,* bl. 63. Londen: Bailliére, Tindall and Cox.

biologic relation between stature and weight; we do not know for instance that the correlation would exist if the population were placed on a different diet'.

In these matters we cannot escape the duty of proving a cause and effect relationship. In the case of smoking and lung cancer this has certainly not been done.

In the present controversy the case made out by the statisticians can only be tested by biological experiment, obviously a very complex task, the difficulty of undertaking which does not justify the premature acrobatic jump to aetiological conclusions to which we have been treated.

An active educational campaign to warn against cigarette smoking (as Berkson points out) seems poorly founded when an examination of the data discloses that cigarette smokers enjoy death rates from cancer equal to or lower than what the general public is experiencing, and that their over-all death rate is also lower.[5]

The case against a causal connexion between cigarette smoking and lung cancer rests on much more than fallacious statistical associations. The investigation is suspect also because of the entirely subjective nature of the data about the amount smoked.

The extreme fallibility of the human memory for research purposes can be illustrated by the human menstrual cycle. Most women are convinced that they can predict the onset of their periods with accuracy. This claim is not surprising, since it is a striking enough phenomenon, with sufficient social inconvenience attached to it to make it appear at first sight as something no woman will reasonably forget about. But when she keeps a calendar 'she soon finds her periods do not appear with the precision she had expected'.[6] This fact has now been established thoroughly by such extensive inquiries that it has led to Fraenkel's dictum: 'The only regularity about the menses is their irregularity.'

In so far as the recollections of the participants in the statistical inquiry can be checked independently and objectively, these recollections are not confirmed. The tobacco consumption figures in Australia (1949-1951) averaged 4.7 to 4.99 lb. per head, compared with the United Kingdom figure of about 5 lb. per head; but in Australia, e.g. in the age group 45-54 years, the incidence of lung cancer was 133 per million as against 555 in the United

5. Berkson, J. (1955): Proc. Staff Meet. Mayo Clin., **30,** 338-339.
6. Hartman, C. G. (1936): *Time of Ovulation in Women,* p. 63. London: Bailliére, Tindall and Cox.

aanleiding gegee het tot Fraenkel se uitspraak: ‚Die enigste reëlmatigheid in verband met die maandstonde is hul onreëlmatigheid.'

Vir sover die herinneringe van die deelnemers aan die statistiese ondersoek op 'n onafhanklike en objektiewe manier gekontroleer kon word, is hierdie herinneringe nie bevestig nie. Die syfers in verband met die verbruik van tabak in Australië vir die jare 1949 tot 1951 was gemiddeld 4.7 tot 4.99 pond per persoon, in vergelyking met die Verenigde Koninkryk se syfer van omtrent 5 pond per persoon; maar in Australië, bv. in die ouderdomsgroep 45-54 jaar, was daar 133 gevalle van longkanker per miljoen teenoor 555 in die Verenigde Koninkryk (1940-1945), en in die ouderdomsgroep 55-64 jaar het die Australiërs 305 gevalle per miljoen gehad in vergelyking met die Verenigde Koninkryk se syfer van 1,116 per miljoen. In Idaho is 2,003 belasting-betaalde sigarette per persoon verkoop, terwyl die sterftesyfer aan longkanker slegs 2.9 was; maar in New York is 2,319 belasting-betaalde sigarette per persoon verkoop, en die sterftesyfer ten gevolge van longkanker was 11.9. Die sterftesyfer ten gevolge van kanker het, met ander woorde, met 400% toegeneem hoewel daar in New York ongeveer net soveel sigarette per persoon as in Idaho verkoop is.[7] Hierdie vergelykende studies toon duidelik aan dat daar geen korrelasie is tussen die hoeveelheid sigarette wat gerook word en die aantal longkanker-sterfgevalle in verskillende dele van die wêreld nie.

Maar selfs al neem ons ook aan dat daar 'n ware vermeerdering in die aantal gevalle van longkanker in die afgelope paar dekades was, moet dit miskien aan ander belangrike oorsake toegeskryf word. Wright van Cardiff het 160 muise 18 maande lank (d.w.s. gedurende die helfte van hul lewe) aan sigaretrook blootgestel. Die ‚rokende' muise het in werklikheid langer as die ‚nie-rokende' muise gelewe. In soverre statistiese teorie dus aan eksperimentele bewyse onderwerp is, ontstaan die suggestie dat die vermoedelike karsinogeniese inasemmiddel bes moontlik nie met die rook van sigarette geassosieer is nie. Dit stem ooreen met die Britse waarnemings, nl. dat daar geen verband is tussen die inaseming van sigaretrook en die ontstaan van longkanker nie.

Hierdie waarneming is beslis afwykend met die oog op die aanspraak dat die moontlikheid dat u aan longkanker sal sterf in regstreekse verhouding staan tot die hoeveelheid tabak wat u rook. Die hipotese berus op die veronderstelling dat daar 'n karsinogenieseinasemmiddel

7. Rigdon, R. H. en Kirchoff, H. (1952): Texas Rep. Biol. Med., **10,** 76.

Kingdom (1940-1945), and in the 55-64 years age group, the Australians had 305 cases per million as against the United Kingdom figure of 1,116 per million. In Idaho 2,003 tax-paid cigarettes were sold per person, while the lung cancer death rate was only 2.9; but in New York there were 2,319 tax-paid cigarettes sold per person and the lung cancer death rate was 11.9. The cancer death rate, therefore, increased 4 times although the number of cigarettes sold per person was about the same in New York and Idaho.[7] These comparative studies establish clearly that there is no correlation between the amount smoked and the number of deaths from lung cancer in different parts of the world.

Even on the assumption that there has been a true increase in lung cancer in recent decades, there are other potent causes which might be operating. Wright of Cardiff exposed 160 mice for 18 months to cigarette smoke (i.e. for half their life span). The 'smoking' mice actually lived longer than the 'non-smoking' mice. In so far as statistical theory has therefore been put to experimental proof, the suggestion arises that the presumed carcinogenic inhalant may well not be associated with cigarette smoking. This is in conformity with the British observations that inhalation of cigarette smoke was unrelated to the production of lung cancer.[2]

This observation is crucially anomalous in view of the claim that the risk of dying from lung cancer is directly proportional to the amount smoked. The hypothesis rests on the assumption that there is a carcinogenic inhalant in cigarette smoke which produces lung cancer. It is therefore an inescapable inference that the incidence of this disease should be greater in inhalers than in non-inhalers. The failure of the extensive British investigation to substantiate this point exposes what must be regarded as a contradiction fatal to the hypothesis which postulates a connexion between cigarette smoking and lung cancer.

Carcinogens extracted from cigarette tobacco smoke have been used experimentally to produce skin cancers on the shaved backs of mice, but not carcinomata in the lungs of Man. In any event, the circumstances of the rodent experiment are not comparable with those in which Man presumably acquires lung cancer. Mouse skin cancer bears no relationship to human cancer and although these experiments are interesting they throw little, if any, light on the human problem. The lungs and the skin have different embryological origins and it cannot be assumed that they will react in

7. Rigdon, R. H. and Kirchoff, H. (1952): Texas Rep. Biol. Med., **10,** 76.

in sigaretrook is wat longkanker veroorsaak. Die gevolgtrekking dat daar meer gevalle van hierdie siekte sal voorkom onder die mense wat die rook inasem as onder die mense wat dit nie doen nie, is dus ewe onvermybaar. Die mislukking van die uitgebreide Britse ondersoek om hierdie punt te staaf, bring dus iets aan die lig wat noodlottig is vir die hipotese wat 'n verband tussen die rook van sigarette en longkanker postuleer.

Karsinogene wat uit die rook van sigarettabak gehaal is, is gebruik om velkanker te produseer op die geskeerde rûe van muise, maar nie karsinomata in die longe van die mens nie. In elk geval, die omstandighede verbonde aan die knaagdiereksperiment kan nie vergelyk word met dié waaronder die mens kwansuis longkanker opdoen nie. Daar is geen verband tussen velkanker by muise en kanker by die mens nie, en hoewel hierdie proefnemings interessant is, werp hulle min indien enige lig op die menslike probleem. Die longe en die vel is van verskillende embriologiese oorsprong, en daar kan nie aangeneem word dat hulle op dieselfde manier op dieselfde prikkelmiddel sal reageer nie. Temeer, velkanker by muise word teweeggebring met behulp van hoogs gekonsentreerde teeruittreksels wat aan die vel aangewend word gedurende die helfte van die leeftyd van die proefdier, en in hoeveelhede en op 'n manier wat nooit voorkom in die longe van 'n sigaretroker nie, selfs al asem hy ook die rook in. Hierdie tydperk van ‚die helfte van die lewe' is deur sommige ondersoekers aangegryp as 'n analogie vir die menslike probleem, en daar word aan die hand gedoen dat die mens ook 'n halwe leeftyd lank moet rook voordat longkanker ontstaan. Hierdie redeneertrant is natuurlik geheel en al misleidend, want nadat die roker 30 jaar lank gerook het, bereik hy onvermydelik die ouderdom waar hy vatbaar vir alle soorte kanker is, of dit nou al in verband staan met die rookgewoonte al dan nie.

'n Ander basiese veronderstelling in die argument is dat daar 'n ware toename in die voorkoms van longkanker in die afgelope paar dekades was. Die statistiese argument berus natuurlik nie op hierdie veronderstelling nie, maar as dit gestaaf kan word, sou dit 'n belangrike hulpargument wees. Rigdon, Kirchoff en Martin[8] wat hierdie aspek van die probleem onlangs weer hersien het, het tot die gevolgtrekking geraak

‚dat die aantal sterfgevalle ten gevolge van longkanker in iedere distrik in verband staan met die aantal geneeshere en die aantal hospitaalbeddens in daardie distrik. Beter diagnose is derhalwe 'n betekenisvolle faktor wat betref die toename in die frekwensie van longkanker.'

Diegene wat bereid is om te glo aan die argument wat ontleen is aan die manipulasie van syfers was miskien die slagoffers van 'n onbewuste numerieke goëltoertjie, want geeneen van die statistiese ondersoeke het die opvallende seldsaamheid van longkanker in plattelandse gemeenskappe verduidelik nie. Afgesien van probleme wat deur verhoogde langlewendheid van die bevolking geskep word, is daar ook die moontlikheid van 'n lugbesmettingsmiddel afkomstig van geteerde paaie, die verbranding van petrol en olie, en die rookprodukte afkomstig van fabrieke wat in die stedelike gebiede gekonsentreer is. Dit kan ons bes moontlik veel gouer op die

8. Rigdon, R. H., Kirchoff, H. en Martin, N. (1955): Texas Rep. Biol. Med., **13,** 162.

the same way to the same irritant. Moreover, skin cancers in mice are produced with highly concentrated tar extracts applied to the skin for half the life span of the experimental animal in a quantity and a manner which never occurs in the lungs of a cigarette smoker, even if he is an inhaler. This period of 'half the life span' has been seized upon by some investigators as an analogy for the human problem, it being suggested that smoking habits must also go on for half a lifetime in Man before lung cancer is produced. This reasoning is, of course, utterly fallacious since after smoking for 30 years, the smoker inevitably reaches an age at which he is vulnerable to cancer of any kind, whether it is connected with smoking or not.

Another basic assumption in the argument is that there has been a true increase in the incidence of lung cancer in recent decades. The statistical argument does not, of course, rest on this assumption, but if it were true, it might be an important ancillary argument. Rigdon, Kirchoff and Martin[8] have recently once again reviewed this aspect of the problem and have concluded that

'the number of deaths from cancer of the lung in each county is related to the number of doctors and the number of hospital beds in the county. Better diagnosis, therefore, is a significant factor in the increase in the frequency of cancer of the lung'.

Those who have accepted the argument derived from the manipulation of numbers may have been the victims of an unconscious numerical sleight of hand, because none of the statistical investigations has explained the extraordinary infrequency of lung cancer in rural communities. Apart from problems created by increased longevity of the population, there is the possibility of an air pollutant derived from tarred roads, the combustion of petrol and oils and the smoky products of factories concentrated in urban areas. This may well provide a more fruitful guide to the carcinogenic inhalant which is sought to be incriminated. It should not be forgotten that the number of lung cancer deaths in English towns has been observed to increase in proportion to the number of chimneys per acre in the town studied, and that 6 tons of tarry material fall on each square mile of Manhattan every year. Argyll Campbell[9] observed an increase in the

8. Rigdon, R. H., Kirchoff, H. and Martin, N. (1955): Texas Rep. Biol. Med., **13,** 162.

9. Ogilvie, R. F. (1951): *Pathological Histology,* 4th ed., p. 141. Edinburgh: E. and S. Livingstone, Ltd.

spoor bring van die karsinogeniese inasemmiddel wat vermoedelik aangekla moet word. Daar moet ook nie vergeet word nie dat die aantal sterfgevalle ten gevolge van longkanker soos in Engelse dorpe waargeneem, toegeneem het in verhouding tot die aantal skoorstene per morg in die dorp wat bestudeer is, en dat 6 ton teeragtige stof iedere jaar op elke vierkante myl van Manhattan uitsak. Argyll Campbell[9] het opgemerk dat die longgewassyfer van 8% tot 80% toegeneem het by muise wat gedwing is om padstof bevattende 2% teer oor 'n lang tydperk in te asem.

Daar steek veel meer in die probleem van longkanker as die oor-vereenvoudigde, ongeoorloofde en verkeerde verduideliking dat dit aan die rook van sigarette te wyte is. Die lokvalle in die weg van diegene wat deur syfers gemesmeriseer word, word pragtig toegelig deur die ondersoek wat deur Doll en Hill[2] ingestel is. Onder hul kontrole-persone was daar in werklikheid meer sonder longkanker (83.3%) as met longkanker (75%) in die groep wat tot 24 sigarette per dag gerook het. Die duidelike gevolgtrekking wat aan die hand van hierdie feit gemaak kan word, is dat middelmatige rookgewoontes in werklikheid 'n meer algemene verskynsel is by persone *sonder* longkanker. Aan die hand van hierdie gegewens sou ons geregtig wees om te argumenteer dat 'n mens tot 24 sigarette per dag kan rook met al die straffeloosheid (en immuniteit) van 'n sigaar- of pyproker. Ons sou selfs geregtig wees om 'n slagspreuk te ontwerp wat min of meer soos volg lui: ‚Hou longkanker op 'n afstand deur 'n pakkie per dag te rook.'

MAN BYT HOND

As ons die begryplike antroposentriese benadering tot hierdie geskil verwerp, kan daar oorweging verleen word aan 'n interessante en insiggewende proefneming wat onlangs op die Filippynse Eilande gedoen is.[10] Garcia (van die Manila Central University) het sap, afkomstig van menslike longkanker, aan die blare van tabakplante gesmeer. Die blare het verwelk en het die slagoffers van uitbreidende nekrotiese letsels geword! Aan die hand van hierdie studie van wederkerige patologie het Garcia tot die gevolgtrekking geraak dat die rook van tabak onskadelik en veilig is, maar dat die kou van tabak nadelige gevolge kan hê. Sy proefnemings vereis natuurlik onafhanklike bevestiging, maar by die behoorlike oorweging van die beskikbare getuienis skyn dit asof Berkson se sorgvuldig oorwoë gevolgtrekking beaam moet word, nl.

„. . . Ek glo nie dat aan die hand van die statistiese studies wat tot dusver onderneem is, ons beslis tot die gevolgtrekking kan geraak dat die rookgewoonte kanker veroorsaak of selfs daarmee „geassosieer" is nie . . . ons is nie geregtig om te konkludeer . . . dat 'n betekenisvolle verband (tussen rook en longkanker) reeds bo alle twyfel bewys is nie. Nog minder glo ek dat die teweegbrengende oorsaak vasgestel is. Ek meen dat daar nie genoeg aandag bestee is aan die moontlikheid dat seleksie die bron van die waargenome assosiasie is nie, dat veel meer werk gedoen sal moet word, en dat meer tyd toegestaan sal moet word vir die waardebepaling van daardie werk, voordat 'n verantwoordelike, definitiewe mening uitgespreek kan word oor die presiese betekenis van die bevindings.'

9. Ogilvie, R. F. (1951): *Pathological Histology*, 4e uitgawe, bl. 141. Edinburgh: E. and S. Livingstone, Ltd.
10. Garcia, E. Y. (1955): MD Journal, **4**, 18.

lung tumour rate from 8% to 80% in mice subjected to the prolonged inhalation of road dust with a 2% content of tar.

There is much more to the problem of lung cancer than the over-simplified, unwarranted and erroneous explanation that it is due to cigarette smoking. The pitfalls that beset those who are mesmerized by numbers are well illustrated by Doll and Hill's investigation.[2] Their controls actually contained more subjects without lung cancer (83.3%) than with lung cancer (75%) in the smoking range up to 24 cigarettes per day. The clear inference from this fact is that moderate smoking is actually commoner in persons *without* lung cancer. On these data we would be entitled to argue that smoking could be indulged in up to 24 cigarettes a day with the impunity (and the immunity) of a cigar or a pipe smoker. We would even be justified in coining the slogan: *A packet a day keeps lung cancer away!*

MAN BITES DOG

If the understandably anthropocentric approach to this controversy is discarded, a recent interesting and instructive experiment conducted in the Philippines can be admitted for consideration.[10] Garcia (of the Manila Central University) smeared the juice expressed from human lung cancers on to the leaves of tobacco plants. These leaves wilted and became the victims of spreading necrotic lesions! From this study in reciprocal pathology Garcia concluded that tobacco smoking was harmless and safe but that tobacco chewing might be injurious. His experiments, of course, need independent verification but there seems little doubt on a proper assessment of the available evidence that Berkson's carefully considered conclusion must be endorsed, viz.

'. . . I do not believe that from the statistical study so far accomplished one can conclude definitely that smoking causes cancer or even that it is "associated" with it . . . it is unwarranted to conclude . . . that a meaningful association has already been proved beyond doubt (between smoking and lung cancer). Much less do I believe that causation has been established. I think that the possibility that selection is the source of the observed association has not been given sufficient weight, and that much more work must be done, and time allowed for its evaluation, before a responsible definite opinion can be had as to the precise significance of the findings'.

10. Garcia, E. Y. (1955): MD Journal, **4**, 18.

VACCINATION AGAINST POLIOMYELITIS

RECENT DEVELOPMENTS

JAMES GEAR, M.B., CH.B.

Poliomyelitis Research Foundation, Johannesburg

It is now over one year since the results of the vast field experiment undertaken in the United States to test the value of a formalin-inactivated poliomyelitis vaccine, prepared according to methods prescribed by Dr. Jonas Salk, were announced by Dr. Francis, head of the evaluation committee. During this time vaccine has been administered on a large scale in the United States of America, Canada and Denmark, and on a more limited scale in South Africa. It is therefore opportune to consider the experiences of the use of the vaccine in these countries, especially as in the future this type of vaccine will become more generally available and medical practitioners will have to decide whether to advise its administration to the children in their care.

UNITED STATES OF AMERICA

Vaccine has been used in the United States on a much greater scale than in any other country. The observations made during the last year have been reported in great detail in a document issued by the United States Public Health Service, the *Progress Report on the Vaccination Program,* released on 24 January 1956. It will be recalled that as a direct result of the field trials with the Salk vaccine carried out by the National Foundation for Infantile Paralysis and in anticipation of a favourable report by the Francis Evaluation Committee, stocks of vaccine tested by the manufacturers were already on hand and the national programme of poliomyelitis vaccination got under way within 2 days after the issue of this report on 12 April 1955.

On 26 April 5 cases of paralytic poliomyelitis were reported in children who had been vaccinated with vaccine produced by the Cutter Laboratories. The following day this company was requested to withdraw its product and thereupon notified its distributors to recover all the vaccine. By 30 April 17 cases of paralytic poliomyelitis had been reported among children injected with the Cutter vaccine and on 8 May the Surgeon General recommended the suspension of the vaccination programme until each manufacturing plant had been visited and its records and procedures inspected. As a result of these visits by officials, vaccine prepared by 2 large companies in the United States was re-cleared for use. An intensive study was made of the Cutter manufacturing plant, its protocols and records, and the completed product, in an effort to determine the cause of the problem. The report of the study was issued on 25 August 1955.

Since the *Minimum Requirements* for poliomyelitis vaccine were first issued on 12 April 1955 by the United States Public Health Service, they have been amended several times. As they are of particular interest to us in South Africa, because our own regulations are based on them, these will be noted. The first amendment to the minimum requirement regulations was concerned with the technical interpretation of the potency requirements. The second amendment, issued on 26 May, imposed more rigid methods of safety testing. These changes in testing procedures required larger volumes of material. A third amendment suggested a new monkey test evolved with the co-operation of various laboratories within the Division of Biological Standards. A fourth amendment insisted on filtration steps designed to remove particulate matter from single strain pools before and during the process of inactivation, and allowed for the use of supplementary inactivation processes. This amendment also introduced modification of the monkey test which emerged from experience since its introduction on 10 September.

The administrative arrangements made to survey the results of the vaccination campaign are also of interest. On 28 April the Surgeon General established the *National Poliomyelitis Surveillance Program* with headquarters at the Public Health Service Communicable Diseases Center in Atlanta, Georgia. The first concern of the Poliomyelitis Surveillance Unit was to evaluate the significance of the cases of poliomyelitis which were occurring among Cutter-vaccinated children and their contacts. Certain characteristics of these cases became evident.

i. There was a concentration in certain geographic areas.

ii. The association with particular lots of vaccine.

iii. The grouping of the onset of most of the cases with appropriate incubation periods following inoculation.

iv. The correlation between the site of inoculation and the site of first paralysis in the majority of vaccinated cases.

Because of these characteristics it was concluded that the development of the disease in some of these patients was the result of the presence in infective amounts of live poliomyelitis virus in some of the lots of vaccine distributed by the Cutter laboratories. Laboratory studies have since supported this conclusion.

Since the revision of safety standards in May 1955, there has been no epidemiological evidence that any lot of vaccine of any manufacturer has been unsafe. Since 13 May all lots of vaccine have been released under revised safety standards. Epidemiological surveillance for possible untoward incidents has been constantly maintained. All States and Territories report on a weekly basis the cases of poliomyelitis which occur among vaccinated children. These are tabulated by lot number so that individual cases associated with the same lot, but occurring in different States, would be promptly recognized. Special attention is directed towards cases which occur at an interval of 4-14 days after inoculation and to paralytic cases showing first paralysis at the site of inoculation. Essential data on each vaccinated case are made available to health authorities. The cases of poliomyelitis reported in vaccinated persons since 1 July have shown certain distinctive characteristics. Over three fourths have been reported as non-paralytic. Most have occurred more than 30 days after vaccination. Those few occurring in the interval 4-14 days did not exceed the normal expectancy of coincidence. Among the relatively infrequent paralytic cases, instances with first paralysis occurring within this interval at the site of inoculation have been rare. Thus, from an epidemiological viewpoint, there is no evidence that use of vaccine has caused poliomyelitis since the adoption of the new safety standards.

Special studies on the effectiveness of the vaccine have also been arranged and the preliminary reports indicate encouraging results even with only one injection of the vaccine. From a study of the reports received from 11 States and one city, it is apparent that the vaccine is of definite value in preventing paralytic poliomyelitis. There is a marked difference between the attack rates for the vaccinated and unvaccinated groups. For paralytic cases the rates are from 2 to more than 5 times greater in the unvaccinated than in the vaccinated groups. The total paralytic rate of the 12 areas combined was 4 times greater in the unvaccinated than the vaccinated group. In the non-paralytic cases no differences were observed in some States; the rate in others for the unvaccinated were 2 or more times greater. The total of children vaccinated in these 11 States was about 2,334,000 compared with some 2,362,000 in the unvaccinated group. Amongst the vaccinated children there were 75 cases of paralytic poliomyelitis compared with 313 cases in the unvaccinated group. Of particular interest are the figures from New York City where, amongst 166,000 vaccinated children, there were 9 cases of paralytic poliomyelitis compared with 19 amongst 87,000 unvaccinated children in the same age group, giving paralytic rates per 100,000 of 5.4 for the vaccinated children and 21.8 for the unvaccinated children. The report concludes by saying that the findings support the conclusion that the vaccine is safe and effective.

The supply, distribution and use of poliomyelitis vaccine is considered in detail, and it is noted that the large-scale production of any new biological product presents initial technical problems which can only be solved through experience and that the problems inherent in the production of this type of vaccine are among the most complex in the field of large-scale biological preparations. It was recognized early that the demand for the vaccine would probably exceed the supply for a number of months. On 14 April the President directed the Secretary of the Department of Health, Education and Welfare, to report to him on the best means of assuring an equitable distribution of the vaccine. The first objective of the Federal Government, after the success of the field trials was announced on 12 April 1955, was to ensure a rapid completion of the National Foundation programme. Finally, this was limited to the purchase of enough vaccine, i.e. of 18,000,000 c.c. for 2 injections for all first and second grade children and for all the participants in the field trials who had received placebo injections. By 13 December 1955 approximately 13,500,000 c.c. of vaccine had been released to the National Foundation. One of the first steps in considering the problem of distributing the vaccine on an equitable basis was the setting up of the National Advisory Committee on poliomyelitis vaccine. The functions of this committee were to make recommendations to the department concerning (1) the best means of ensuring an equitable distribution of the vaccine; (2) the age groups which should be given priority because of their greater susceptibility to poliomyelitis; and (3) broad problems which relate to the distribution and the use of the vaccine. The Committee is composed of representatives of the medical and pharmaceutical professions, the Public Health Administration and the general public.

During the early months of the programme, when the demand for the vaccine far exceeded the supply, the National Advisory Committee recommended that its administration be restricted to children in the 5-9 year age group. This group was at the greatest risk. However, this Federal age group priority was not binding on the States so far as the inter-state allocation and use of the vaccine was concerned. Nevertheless, once the vaccine had been allocated to the States on the basis of those age groups, with few exceptions, States and Territories followed the recommendations of the Committee and established as their first priority these children of the 5-9 year age group. By early October 1955 the vaccine supply was approaching fulfilment of the demand for 2 injections each to the 5-9 age group. Almost 24,000,000 c.c. of vaccine had been released by the Public Health Service, enough to give 2 injections to three fourths of the 16,000,000 children in this age category. In order to expedite prompt use of the vaccine, many States recommended to the Service that the priority group be enlarged so that vaccination might be extended to additional ages, and on 12 October the Secretary of the Department of Health, Education and Welfare brought the priority group to receive poliomyelitis vaccine so that it could include persons from 0-14 years, and pregnant women. Because the vaccine was still short of the total demand, the Secretary further recommended that each State initially extend its priority group to embrace no more than 5 additional years of age outside the original 5-9 year age priority group and, if so desired, to include pregnant women. As the difference in susceptibility varied from State to State, the broadened priority group similarly varied.

Recognizing the importance of rapidly protecting as many children as possible from poliomyelitis, the President, in April, stated his belief that Federal funds should be appropriated to assist in the vaccination programme, and the Secretary of the Department of Health submitted to Congress a proposed *Poliomyelitis Vaccination Assistance Act of 1955* which, with substantial amendments, was enacted. Congress has appropriated $30,000,000 to carry out the purposes of this Act. Of this total amount $25,000,000 is available to the States for the vaccine only. Adequate funds have thus been made available to provide vaccine to all those children in the United States who need it, and it is obvious that within a very short time nearly all children under the age of 20 will have been vaccinated in the United States of America. The result of this vaccination campaign has been most favourable in the first years of observation.

CANADA

In Canada production of poliomyelitis vaccine was undertaken by the Connaught Laboratories, Toronto. The Maitland tissue culture technique, using rhesus monkey kidney tissue, was employed. The strains of virus were the same as those used by the American manufacturers, viz. the Mahoney strain as representative of Type 1, the M.E.F. strain as representative of Type 2, and the Saukett strain as representative of Type 3. These are all virulent strains and it is of particular interest to note the inclusion of the Mahoney strain as the representative of Type 1. The vaccine before issue was required to conform with the Minimum Requirements of the National Institute of Health of the United States Public Health Service.

The vaccine was purchased by the Department of National Health and Welfare and the provincial departments of health. It was distributed to the provincial departments of health to their regional medical officers, who organized and supervised the vaccination programme.

Approximately 860,000 children between the ages of 6-9 years were inoculated with the vaccine. Most received 2 doses, given subcutaneously at an interval of 4 weeks. About 100,000 children received the vaccine intramuscularly. Three cases of paralytic poliomyelitis were reported in children within 4 weeks of vaccination. In only one of these was there a possible relationship between the vaccination and the disease.

The incidence of poliomyelitis in Canada last year was lower than for many years past, and it therefore has been difficult to judge the effectiveness of the vaccine. However, preliminary results indicate that cases of paralytic poliomyelitis were 5 times as frequent in unvaccinated children as in vaccinated children.

DENMARK

Denmark's experience of the vaccine has been almost as great, relatively, as that of the United States. The Scandinavian countries have suffered severely from epidemics of paralytic poliomyelitis, and the worst epidemic experienced in Denmark occurred in the Autumn of 1952, with 2,450 paralytic cases. More than half these cases occurred in the metropolitan area of Copenhagen, with 1,000,000 inhabitants. The epidemic was also characterized by the severity of clinical illness; about 20% of the paralytic cases were bulbar, with a fatality rate of 50%. It was therefore

with considerable relief that the Danish welfare authorities welcomed the vaccination programme made possible by the development of a formalinized type of vaccine. This was produced at the Danish State Serum Institute according to the method described by Salk. The virus growths necessary for the preparation of vaccine were prepared in tissue cultures of trypsinized monkey tissue. Strains used in preparing the vaccine were, respectively, the Brunhilde, as the representative of Type I, M.E.F. 1 as the representative of Type 2 and the Saukett strain as representative of Type 3. The Brunhilde strain was preferred to the Mahoney strain, which was used in the American vaccine, because of its lesser virulence on peripheral inoculation. In Denmark the laboratory responsible for production of the vaccine was also responsible for the control, and the safety tests were somewhat more elaborate than those required at the time by the United States Public Health Service.

Unlike most of the vaccine produced in America, no preservative was added to the Danish vaccine and the pooled trivalent vaccine was filtered through glass filters and distributed in ampoules as soon as possible after filtration. The vials are kept at room temperature for 2 weeks and checked individually for visible contamination before labelling, storage in an ice box and issue. In spite of the lack of preservative, contaminated ampoules were found very rarely.

The vaccine was given intradermally in the fore-arm, 2 injections of 0.1-0.15 ml. each, resulting in 2 papules with a diameter of about 8 mm. This procedure was repeated after 4-6 weeks and a third injection will be given 9-12 months after the first.

No cases of paralysis occurred in the vaccinated children; in fact no case of paralytic poliomyelitis occurred in Denmark in the spring and early summer. The reactions following the administration of the vaccine by the dermal route were mild and infrequent, consisting mainly of local swelling of the arm at the site of inoculation. The preliminary estimate indicates that this occurred in 0.1-0.2% of the children. In all cases where illness, fever, headache and miscellaneous symptoms were suspected of being associated with the vaccine inoculation, stool and serum samples were obtained from the child. None of these stool samples from a total of 42 children was found to contain poliovirus.

In order to study the antibody response in children, sera were collected from children from 2 sections of Copenhagen as well as from cities and rural districts in other parts of the country. Blood samples were obtained from approximately 2,300 children. The preliminary screening of 2,000 of these pre-vaccination serum samples using undiluted serum in the neutralization test has been carried out. It was found that 13% of these 8-year-old children had no antibodies to any of the 3 types of poliovirus. Antibodies to all 3 types were found in 24% of the sera. Since the second inoculation of the vaccine was given 4 weeks later, before the beginning of the school summer vacation, the post-vaccination sample was usually not taken until August. Paired serum samples from 48 children who did not have antibodies against Type I poliovirus were chosen for a preliminary study. The response, as regards formation of antibodies to Types 2 and 3, was good. Of 27 children without antibodies to Type 2 before vaccination all but one developed Type 2 antibodies. That is a response of 96%. As regards Type 3, all 23 children without Type 3 antibodies before vaccination showed Type 3 antibodies after. The response was 100%. The Type I response was less satisfactory. Out of 48 children, 29 (60%) developed antibodies to this type. Of 12 without antibodies to any of the 3 types only 4 developed Type I antibodies after vaccination.

As the incidence of poliomyelitis was very low last year, no field evaluation of the vaccine was possible. There were no cases amongst the vaccinated children.

BRITAIN

The position taken up by the British Medical Research Council has been of considerable interest and many authorities have looked to them for a guide as to what to do about vaccination. Soon after the 'Cutter incident', Dr. G. S. Wilson, a leading authority in Britain, announced that the British Government would not authorize the release of the Salk-type vaccine. This statement gave rise to considerable misunderstanding and in a subsequent explanatory statement it was emphasized that what Dr. Wilson meant was that the Medical Research Council would not authorize the use in Britain of a formalinized type of vaccine containing the virulent Mahoney strain. The initiation of vaccination in England was thus delayed for a full year. However, during that year a considerable amount of work has been carried out to determine the value of other, less virulent strains of virus, in preparing poliomyelitis vaccine.

Two well-known commercial firms are at present producing poliomyelitis vaccine in Britain. The strains of virus incorporated in

the vaccine are different from those at present incorporated in the vaccine made in the United States. As represenative of Type I poliovirus, both British manufacturers are using a variant of the Brunhilde strain, originally isolated by Howe and Bodian, and later modified and partially attenuated by Enders and Sabin. This strain is much less virulent than the Mahoney strain, which was used in the original Salk vaccine. Dr. Perry, the head of the Biological Control laboratory in Britain, has stated that before the new vaccine could become dangerous it would almost certainly have to contain enormous quantities of virus which had escaped inactivation and he notes further, that with the methods of production now in use, it is in the highest degree unlikely that such an accident could occur; and if it did, it is practically beyond the bounds of possibility that it would escape detection by the stringent safety tests which are applied to all batches of vaccine. As the representative of Type 2 virus one British manufacturer is using the M.E.F. 1 strain, that was originally, and is still, incorporated in the United States vaccine, the other is using the Y.S.K. strain described by Sabin, which is also of low virulence. As representative of Type 3 strain of poliovirus, one British manufacturer is using the Saukett strain, which was originally, and still is, incorporated in the United States vaccine, the other is using the Leon strain, also described by Sabin and also of low virulence. Like the vaccine produced in the United States, all British vaccine is grown on monkey kidney tissue by methods similar to those used in the United States and elsewhere. The virus suspension is inactivated with formalin, the method being virtually identical with that in use in the United States of America; 100 units of penicillin and 100 micrograms of streptomycin are added during the preparation of these tissue cultures, per c.c. During inactivation with formalin the virus suspension is maintained at a temperature of 37° for 12 days at a pH of 7. Under these conditions penicillin is so labile that little should remain. Assays are difficult, but what remains is less than 0.5 units per ml. As least 99.5% of the penicillin has been destroyed. Of the streptomycin, 95% has been destroyed. It is therefore considered that sensitization to either of these antibiotics is very unlikely as a result of the use of the vaccine.

The safety tests are similar to those in use in the United States but are even more comprehensive. After being safety-tested at the manufacturer's laboratory, all batches of vaccine are also submitted to the full series of safety tests in the Biological Control Laboratory, which has been set up by the Medical Research Council in the National Institute of Medical Research at Hampstead. The aims of these safety tests, as with the safety tests elsewhere, are to exclude vaccine containing living organisms other than poliovirus and also to detect by tissue culture and by monkey inoculation live poliovirus. The potency of the vaccine has been determined by monkey inoculation. The guineapig test has also been studied. It will be clear then, that although the British vaccine is essentially similar to that described as the Salk vaccine, and follows almost exactly the methods of preparation prescribed by Salk, it has the essential difference that it is made from strains which are known to be less virulent than the Mahoney strain, the strain which was responsible for the incidents in the United States. It is hoped that this vaccine will be safer, and there is every ground for believing that that hope will be realized. How effective the vaccine is compared with the vaccine containing the Mahoney type virus is not known and of course it will be extremely difficult to find out, and only many years of experience of its use in actual practice will provide an answer to this important question.

SOUTH AFRICA

Until recently South Africa was one of the few countries in a position to produce poliomyelitis vaccine. The accommodation in the form of the Laboratories of the Poliomyelitis Research Foundation and the equipment was provided by the Board of Trustees, appointed to administer the Poliomyelitis Research Fund, subscribed by the public of Southern Africa. The methods of production of the poliomyelitis vaccine prepared in the Laboratories of the Poliomyelitis Research Foundation has been discussed by Turner[1] and, more recently, by Gear.[2] There is, therefore, no need to describe them in detail. In general, the methods follow those described by Salk and his associates. However, the strains of virus representing the 3 types of poliovirus are different from those incorporated in the American vaccine. Originally the 3 types were represented by the Brunhilde virus as the representative of Type I poliovirus. This virus was chosen in preference to the Mahoney strain as the latter was known to be unusually virulent even on peripheral inoculation in minute amounts. It will be recalled that in the Danish vaccine, the Brunhilde strain was preferred to the Mahoney strain for the same reasons. Type 2 poliovirus was represented by the Collans

strain, which was isolated by Prof. M. van den Ende in Cape Town from the central nervous system of a fatal case in an adult. The type 3 was represented by the Templeon strain isolated by Dr. H. H. Malherbe of these laboratories from the faeces of a child, one of a number of children found to have silent infections who had been in contact in a nursery school with a child who died of bulbar poliomyelitis.

These strains were originally chosen as it was found that they regularly gave prolific growths of virus in tissue culture. However, they are virulent strains and last year it was decided to substitute for them less virulent strains. These were obtained from Dr. Albert Sabin, who has made a special study of their properties. These strains are not entirely non-virulent, for some monkeys after intraspinal inoculation develop weakness or paralysis and show the lesions of poliomyelitis in the spinal cord. However, they are much less virulent than those hitherto used both in this country and in the United States.

The virus is grown in tissue cultures of kidney cells obtained from the common South African vervet monkey *Cercopithecus aethiops pygerythrus*.

The method of inactivation with formalin has been slightly modified and in recently prepared batches has been supplemented by treatment with ultraviolet light. These modifications were introduced to ensure greater safety.

Before issue the vaccine is required to conform with the minimum standards for potency and safety laid down by the Union Health Department.

ADMINISTRATIVE ARRANGEMENTS FOR THE CONTROL OF POLIOMYELITIS VACCINE

Recognizing its importance, the Minister of Health assumed responsibility for the control of the issue of the vaccine. A committee of public health and virus experts was appointed to advise him on all matters affecting the vaccine. This committee has met on several occasions and, after full consideration of all the information available, recommended in August 1955 that the South African vaccine should be released for issue. For various reasons it was not anticipated there would be much demand for the vaccine. However, the demand exceeded the supply and a Priorities Committee was appointed to advise the Minister on the allocation of the available vaccine. It was recommended that this should be restricted to children under the age of 6 and children of doctors, nurses and other health officials, up to the age of 16 years.

Results of Vaccination. About 16,000 doses were issued and it is estimated that about 15,000 children were vaccinated with the first dose of vaccine in August and September. The issue of the second dose was postponed because the vaccine, which had been ampouled ready for issue and had passed the tests for the Minimum Requirements then in force, had not undergone the tests of the latest requirements subsequently introduced by the United States Public Health Service.

No cases of paralytic poliomyelitis attributable to the vaccine were reported. Of 6 untoward reactions reported, 2 proved to be due to coincidental infection. Two children developed a rash, possibly allergic in origin, and 2 complained of numbness and weakness of the limbs within the week following vaccination.

The antibody response of a group of 60 children following vaccination was found to be satisfactory in that all, except one, developed the antibodies against poliovirus lacking before vaccination.

In a group of another 15 children, 8 lacking Type 1 antibodies before vaccination developed them subsequently. Six lacking antibodies to Type 2 virus developed them subsequently, and of 9 lacking antibodies to Type 3, seven developed them and 2 did not, after vaccination.

The number of children inoculated is too small to draw conclusions about the protective value of the vaccine. However, unlike Canada and Denmark, poliomyelitis again became epidemic in the following season. During this epidemic 4 children who had been vaccinated developed an illness suspected of being poliomyelitis. In none of these has the diagnosis yet been confirmed by the isolation of the virus. In 4 families which were known to be infected, 4 unvaccinated children developed paralytic poliomyelitis, while 9 vaccinated children remained well.

Conclusion. Although limited, the experience of the use of the South African vaccine, as far as it has gone, is encouraging. When considered with the much greater experience in the United States, Canada and Denmark, the conclusion may fairly be come to that a formalin-inactivated vaccine against poliomyelitis, conforming with the required standards, is safe and is effective in preventing the majority of cases of paralytic poliomyelitis, which would have occurred in the absence of the protection conferred by vaccination. How-

ever, it should be clearly understood that this experience covers one or two years only. It will not be known how effective the vaccination has been until the children inoculated have grown from infancy to adulthood and passed through those years of life when they are most susceptible to paralytic poliomyelitis.

OPSOMMING

Die geskiedenis van inenting teen poliomiëlitis in die Verenigde State van Amerika, Kanada, Denemarke, Brittanje en Suid-Afrika word deur die skrywer in oënskou geneem.

Hy geraak tot die gevolgtrekking dat 'n entstof wat met behulp van formalien onaktief gemaak is, voorberei kan word, en dat so 'n entstof veilig en doeltreffend sal wees vir die voorkoming van die meeste gevalle van paralitiese poliomiëlitis.

Hy beklemtoon egter dat die doeltreffendheid van die entstof nie vasgestel kan word totdat die kinders wat ingeënt is, opgegroei het en die jare wanneer hulle veral vatbaar vir die paralitiese vorm van poliomiëlitis is, agter die rug het nie.

REFERENCES

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2. Gear, J. (1956): S. Afr. Med. J., **30,** 587.

NOTES AND NEWS · BERIGTE

Dr. J. E. Wolff, of Johannesburg, left towards the end of June by air for Rio de Janeiro where he will join Professor Franceschetti at the invitation of Professor Nelson Maura Brazil.

Dr. Wolff will be back in Johannesburg at the beginning of September.

* * *

Mr. Paul Marchand, Ch.M., F.R.C.S. (Eng.), is now in partnership with Mr. L. Fatti, F.R.C.S. (Eng.), and will practice as a consultant thoracic surgeon at the Princess Nursing Home, Esselen Street, Hillbrow, Johannesburg. (Telephones: *Rooms*: 44-1955; *Residence*: 48-8809.)

* * *

Mr. F. J. Hedden, B.Sc., M.B., B.Ch. (Wales), F.R.C.S. (Eng.), F.R.C.S. (Ed.), has commenced practice as an orthopaedic surgeon at 202 Medical Centre, Voortrekker Street, Germiston. (Telephones: *Rooms*: 51-1935, 51-2007; *Residence*: 44-3936.)

* * *

Dr. A. Luntz, formerly on the staff of Tara Hospital, Johannesburg, left on 4 June by air for Sydney, Australia, to assume duties as a Consultant in Hospital Planning. Dr. Luntz will work in association with Sir Arthur Stephenson, who visited the Union two years ago.

Dr. A. Luntz

Dr. Luntz qualified at Liverpool University as an architect before he took up a medical career. His first task in Sydney will be to design the new Medical School for the University of Sydney.

* * *

Dr. Peter A. Caswell, M.B., B.Ch. (Rand), D.A. (R.C.P. & S.) Ireland, D.A. (R.C.P. & S.) England, specialist anaesthetist, has joined Drs. G. Hochschild, F. W. Roberts and M. S. Kramer in partnership at 309 Harley Chambers, Jeppe Street, Johannesburg. (Telephones: *Rooms*: 22-8614, 22-6553; *Residence*: 41-2432.)

* * *

Dr. Eric Samuel has left for an overseas visit to deliver a Hunterian professorial lecture to the Royal College of Surgeons. Dr. Samuel will also lecture at the Karolinska Hospital, Stockholm and will attend the Faculty of Radiologists' meeting at Cambridge and the International Congress of Gastroenterology in London.

* * *

Prof. T. Gillman, Head of the Department of Physiology, Faculty of Medicine, University of Natal, and co-director of the Schlesinger Organization Medical Research Unit established by Mr. John Schlesinger in the Department of Physiology, Durban, has been invited by the Council for the International Organization of Medical Sciences of UNESCO and WHO to attend a meeting of experts for the informal discussion of the structure and functions of normal connective tissues. Other experts will attend from the following countries: United States of America, United Kingdom, South America, Canada, Sweden, Denmark, France, Germany, Italy, and Russia. The Conference will be held in London from 20-24 July.

Prof. T. Gillman

Professor Gillman will also attend the *Third Ciba Foundation Colloquium on Ageing*, to be held in London from 25-26 July.

At the end of July he will leave for the Continent to attend in Amsterdam a joint meeting of the British Society for Research on Ageing and the Dutch Gerontology Association and the International Physiological Congress in Brussels. On his way to South Africa he will break his journey at Rome to be present at a meeting of one of the sub-committees of the International Council for the Study of Cancer, to which he was appointed two years ago.

Professor Gillman will also visit the Makerere Medical School at Kampala. This will give him the opportunity to study problems of medical education peculiar to such institutions as the Durban Medical School; and he will have the opportunity of meeting Prof. G. W. Gale, formerly Dean of the

Medical School in Durban and a former Union Secretary of Health.

Professor Gillman will be back in South Africa by 18 August 1956.

PARENTERAL FLUID THERAPY: A CONCISE GUIDE

An extremely valuable and practical guide to parenteral therapy has just been published by Saphar Laboratories Limited, P.O. Box 256, Johannesburg.

The problems of surgery, burns and dehydration are dealt with in adults and children and special attention is directed to calorie requirements and fluid and electrolyte losses.

Useful tables of solutions and milliequivalents, normal blood values, and the electrolyte composition of milk are included.

This concise guide will be of particular help to students and interns. Those interested in obtaining copies should communicate with the publishers at the address given.

FIRST INTERNATIONAL CANCER CYTOLOGY CONGRESS

This Congress (as announced in our issue of 7 July 1956) will be held at the Drake Hotel, Chicago, Illinois, U.S.A., from 9-11 October 1956.

The detailed programme is as follows:

9 *October* 1956—*Morning* (*Chairman*: *Charles S. Cameron, New York*).

The Historical Landmark in Exfoliative Cytology (*G. N. Papanicolaou*).

The Present-Day Scope of Clinical Cytology (*John B. Hazard*).

Structure of the Fixed and Stained Cell (*Isadore Gersh*).

Possibly Distinctive Properties of Malignant Cells (*E. V. Cowdry*).

Normal Cells Originating in the Respiratory Tract (*Eileen King*).

Pulmonary Cancers and Their Cells: A Study of Sputum (*J. B. McDonald and L. B. Woolner.*)

Pulmonary Cancers and Their Cells: A Study of Bronchial Washings (*N. C. Foot*).

Afternoon (*Chairman*: *David A. Wood, San Francisco*).

The Cellular Content of Effusions not Related to Cancer (*Sarah Luse*).

Recognition of Malignant Tumour Cells in Effusions (*Otto Saphir*).

The Cellular Detection of Carcinoma of the Oesophagus (*F. T. Gephart*).

Normal and Abnormal Cells in Gastric Washings (*John Seybolt*).

The Cellular Detection of Cancers Involving the Urinary Tract (*W. T. Wikle*).

A Pathologist's Views on the Subject of Cytology (*D. C. Dahlin*).

Panel Discussion: Aspiration Biopsy. *Moderator*: John T. Godwin.

Panelists: Guy F. Robbins, William G. Bernhard, John Berg.

10 *October* 1956—*Morning* (*Chairman*: *Lewis C. Scheffey, Philadelphia*).

Problems in Mass Screening (*C. C. Erickson*).

The Automatic Scanner (*W. E. Tolles*).

Normal Cells Arising in the Female Genital Tract (*C. M. Street*).

Metaplasia of the Uterine Cervix (*H. F. McCorkle*).

Atypia of the Uterine Cervix and Its Relation to Trichomoniasis (*T. R. Simon, L. G. Koss and W. Wolinska*).

'Pre-Cancerous' Changes in the Uterine Cervix (*E. E. Siegler*).

Panel Discussion: Problems in Confirming Cellular Evidence of Cancer. *Moderator*: Clyde L. Randall.

Panelists: Saul B. Gusberg, Roger B. Scott, Frank W. Hartman.

Afternoon (*Chairman*: *Osborne A. Brines, Detroit*).

Cellular Changes Simulating Those of Cancer (*R. M. Graham*).

Cellular Study of Epithelial Dysplasia in Pregnancy (*W. D. Walters*).

Squamous Cell Cancer of the Uterine Cervix: A Histo-Cytological Study (*J. L. McCormack*).

The Cellular Detection of Uterine Adenocarcinoma (*John Berg and Grace R. Durfee*).

Panel Discussion: Prognosis in Cancer of the Uterine Cervix as Determined by Histologic and Cytologic Methods. *Moderator*: John B. Graham.

Panelists: A. Glucksman, R. H. Fennell, Jr., Ralph Kendall, R. Graham, A. M. Nielsen.

11 *October* 1956—*Morning* (*Chairman*: *Emerson Day, New York*).

New Advances in Cytology (*Papers to be selected*).

Afternoon (*Chairman*: *J. B. McNaught, Denver*).

Symposium: Carcinoma *in situ* of the Uterine Cervix. *Moderator*: Arthur T. Hertig, Boston.

Participants: L. D. Stoddard, J. L. McKelvey, P. A. Younge, H. Kottmeier, J. W. Reagan, E. Von Haam.

TREATMENT OF ARTHRITIS

The succinate-salicylate preparation (Bermide) used by the author* in 30 patients with rheumatoid arthritis and in 30 patients with osteoarthritis contains 0.18 g. of calcium succinate and 0.24 g. of acetylsalicylic acid per tablet. Twenty-four tablets were administered daily (in 4 equal doses) for 21 days; then 16 tablets for 30 days or until a remission in the rheumatoid joints occurred; then 12 tablets for 30 days; and finally a maintenance prophylactic dose of 4 tablets daily.

The report states that mild relapses occurred in only 2 patients, and then the dosage was increased to 24 tablets daily for one week, after which dosage was reduced. Dr. Gilpin found that succinate-salicylate proved to be an excellent therapeutic agent in correcting the signs and symptoms in both osteoarthritis and rheumatoid arthritis. Side-effects were fewer than might be expected with acetylsalicylic acid alone. Use of the combination of calcium succinate and acetylsalicylic acid proved far superior to use of acetylsalicylic acid alone as regards not only toxicity but also for therapeutic results. The sedimentation rates in patients with rheumatoid arthritis rapidly became normal and remained so.

Prothrombin rates did not change. Results were lasting and apparently affected the disease process itself over the 2-year follow-up. Succinate-salicylate (Bermide) therapy did not require as much supervision as do other treatments, e.g. the administration of corticotrophin, cortisone or gold.

Dr. Gilpin concluded that succinate-salicylate is the treatment of choice in early arthritis when salicylates are indicated.

* Gilpin, W. A. (1955): J. Mich. Med. Soc., **54**, 1428. (Also abstracted in J. Amer. Med. Assoc., 7 April 1956, p. 1261.)

PENISILLIEN-V: VERSLAG OOR 'N KLINIESE TOETS*

Hierdie verslag handel oor die gebruik van Distaquaine V (fenoksimetielpenisillien) wat in vergelyking met vloeibare kristal-penisillien wat deur middel van spierinspuitings toegedien word, aangewend is. Gevalle is sonder uitsoek en sonder onderskeid om die beurt met Distaquaine V wat mondeling, en vloeibare kristalpenisillien wat deur middel van spierinspuitings toegedien word, behandel.

Daar word 'n getabelleerde opsomming van die resultate wat met 24 pasiënte verkry is, aangegee, en heelwat besonderhede word verstrek. Die tabelle gee die ouderdom van iedere pasiënt, die geslag, die diagnose, die aanvanklike temperatuur, die hoeveelheid wit bloedliggaampies wat in die begin aanwesig is, die oorheersende organismes wat afgesonder is, die aanvanklike X-straalopname van die borskas, die tydperk wat daar koors was, die getal dae wat die pasiënt in die hospitaal gebly het, die finale hoeveelheid witbloedliggaampies, die finale X-straalopname van die borskas, bygevolge wat waargeneem is, en algemene kommentaar. Uit hierdie gegewens en gegewens wat daarna van ander pasiënte verkry is wat aan infeksies van die asemhalingsorgane gely het, is die volgende afgelei:

1. Die pasiënte gee sonder twyfel voorkeur aan mondelinge toediening bo spierinspuitings.

2. Die paar bygevolge is onbeduidend. Die enigste bygevolge wat waargeneem is by die groep aan wie penisillien mondeling toegedien is, is seerheid van die tong wat by party gevalle twee dae lank aangehou het. Daar het geen gevalle van diarree en allergie voorgekom nie.

3. Sover dit geneeskundige doeltreffendheid betref, is daar blykbaar min verskil tussen penisillien wat mondeling of deur middel van spierinspuitings toegedien word.

4. Van die getabelleerde gevalle het mense wat spierinspuitings ontvang het, altesaam 261 dae in die hospitaal deurgebring, terwyl die totale getal dae vir die gevalle wat deur middel van mondelinge toediening behandel is, 229 dae was. Die syfers ten opsigte van die duur van koors by gevalle onder geneeskundige behandeling, is 36½ dae vir gevalle wat met spierinspuitings en 32½ dae vir gevalle wat met mondelinge toediening behandel is.

Die skrywers verklaar dat die klein verskil in albei gevalle daaraan te wyte is dat daar twee gevalle van long- en lugpypontsteking by die groep wat met spierinspuitings behandel is, ingesluit is. Nadat hulle verklaar het dat die nuwe penisillien-V wat mondeling toegedien word ‚belowe om 'n uiters nuttige, doeltreffende en gewilde geneeskundige wapen te wees', som die skrywers hulle bevindings soos volg op:

‚Die resultate wat behaal is met hierdie aanvanklike klein getal pasiënte wat volgens roetine in dieselfde twee siekesale in hierdie hospitaal opgeneem is, laat ons die verwagting koester dat ons hier 'n nuttige en praktiese alternatief het vir penisillien wat parenteraal toegedien word, en dit behoort veral by die bedrywige algemene praktyk besonder nuttig te wees'.

* F. Dudley Hart, M.D., F.R.C.P., Denis Burley, M.B., B.S., Roger Manley, M.B., B.S., en George Brown, M.B., B.S. (1956): Brit. Med. J., **1**, 496.

COLLEGE OF PHYSICIANS AND SURGEONS OF SOUTH AFRICA

The result of the Ballot for the election of the First Council of the College of Physicians and Surgeons of South Africa was as follows:

1.	Elliott, G. A.,	297	Associate Founder, Tvl.
2.	McMurray, T. B.,	256	Founder, Cape
3.	Forman, F.,	230	Associate Founder, Cape
4.	Brock, J. F.,	158	Associate Founder, Cape
5.	Trubshaw, W. H. D.,	156	Founder, Tvl.
6.	Crichton, E. C.,	153	Associate Founder, Cape
7.	Sichel, A. W. S.,	152	Founder, Cape
8.	Theron, R.,	152	Founder, O.F.S.
9.	Sweetapple, A. G.,	141	Founder, Natal
10.	Douglas, J. A.,	137	Founder, Tvl.
11.	Suzman, M. M.,	126	Founder, Tvl.
12.	Louw, J. H.,	126	Associate Founder, Cape
13.	Heymann, S. C.,	116	Founder, Tvl.
14.	Helfet, A. J.,	113	Founder, Cape
15.	Marr, J. A. S.,	111	Founder, Cape
16.	Kark, A. E.,	111	Associate Founder, Natal
17.	Shapiro, M.,	108	Founder, Tvl.
18.	de la Hunt, N. E. C.,	107	Founder, Tvl.
19.	Schneider, T.,	103	Founder, Tvl.
20.	Reid, F. P.,	95	Founder, Tvl.
21.	Coetzee, J. C.,	93	Founder, Cape
22.	Schabort, J. W.,	91	Founder, Tvl.
23.	Tonkin, A. H.,	89	Founder, Cape
24.	te Groen, L. J.,	85	Associate Founder, Tvl.
25.	Crichton, D.,	84	Founder, Natal
26.	Daubenton, F.,	79	Founder, Tvl.
27.	Kark, W.,	79	Founder, Tvl.
28.	Connan, P.,	77	Founder, O.F.S.
29.	Archer, B. W. C.,	72	Founder, Natal
30.	du Toit, J. S.,	68	Founder, Cape
31.	Wolfowitz, J.,	65	Founder, Tvl.
32.	Marais, D. P.,	65	Founder, Cape
33.	Geerling, R.,	61	Founder, Tvl.
34.	Sacks, I.,	59	Founder, O.F.S.
35.	Brayshaw, H. C.,	58	Founder, Tvl.
36.	Armitage, B. A.,	50	Founder, Natal
37.	Goldberg, S.,	50	Founder, O.F.S.
38.	Savage, H. B.,	49	Founder, Natal
39.	Feldman, M. B.,	44	Founder, Tvl.
40.	Smyth, G. S.,	44	Founder, Tvl.
41.	Wagner, P. F. H.,	41	Founder, Cape
42.	Hochschild, G.,	40	Founder, Tvl.
43.	Sandler, E. M.,	33	Associate Founder, Cape
44.	Lombard, W. A.,	24	Founder, Tvl.
45.	Bischoff, E. W.,	12	Founder, Tvl.

The First Council was therefore elected as follows:

Brock, J. F.	Douglas, J. A.
Forman, F.	Elliott, G. A.
Helfet, A. J.	Heymann, S. C.
McMurray, T. B.	Suzman, M. M.
Sichel, A. W. S.	Trubshaw, W. H. D.
Theron, R.	Sweetapple, A. G.

PREPARATE EN TOESTELLE

CORDEX-TABLETTE

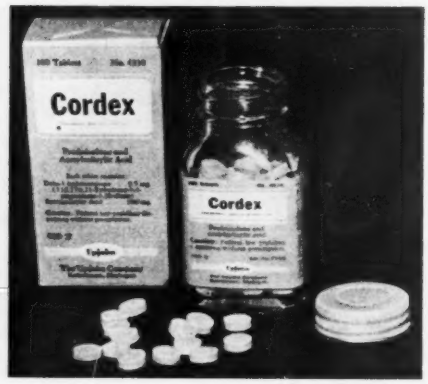
VIR LIGTE TOT MIDDELMATIGE RUMATIEK-TOESTANDE

Iedere tablet bevat:

Delta-1-hidrokortisoon ... ... 0.5 mg.
(11b, 17a, 21-trihidroksi-1, 4-pregnadiene-3, 20-dioon)

Asetielsalisielsuur ... ... 300 mg.

Beskrywing: Cordex-tablette waarin die anti-ontstekings- en rumatiekbestrydende effek van delta-1-hidrokortisoon verenig is met die pynstillende uitwerking van asetielsalisielsuur, is ontwerp in die eerste en vernaamste plaas vir gebruik deur pasiënte wat aan ligte tot middelmatige rumatiekkwale ly.



Indikasies: Cordex-tablette word aangedui vir die volgende ligte tot middelmatige toestande wat nie langer deur salisilate alleen gekontroleer kan word nie: chroniese gewrigsontsteking, been- en gewrigsontsteking, jigagtige gewrigsontsteking, slymbeursontsteking, peessynovitis, miositis, fibrositis en senuwee-ontsteking.

Dosis: Die gewone dosis is 1 tot 2 tablette 4 maal per dag, met 'n maksimum-dosis van 3 tablette 4 maal per dag. Vir optimum-voordele, veral by pasiënte wat waarskynlik oor 'n lang tydperk behandel sal moet word, moet die aanvangsdosis gebaseer word op die pasiënt se verdraagsaamheidsvermoë vir sover dit asetielsalisielsuur betref. Die aanvanklike dosis moet voortgesit word totdat daar 'n bevredigende kliniese reaksie is. Dan word die dosis tot die minimaal doeltreffende peil verminder. Om die moontlikheid van maagprikkeling sover doenlik uit te skakel, behoort iedere dosis onmiddellik na 'n maaltyd en met slapenstyd geneem te word.

Die maksimum-dosis van 3 Cordex-tablette 4 maal per dag verskaf 6 mg. delta-1-hidrokortisoon, en die ontwikkeling van onwenslike hormoonreaksies is derhalwe onwaarskynlik. Nietemin behoort pasiënte wat Cordex-tablette neem, sorgvuldig dopgehou te word, en dieselfde voorsorgmaatreëls as in die geval van ander vorms van adrenokortikoïed-terapie behoort toegepas te word.

Verpakking: Cordex-tablette word verpak in hoeveelhede van 24 en 100.

Verspreiders: Westdene Products (Pty.) Ltd., Essanby-gebou 22-24, Jeppestraat 175, Johannesburg.

EQUANIL

MEPROBAMATE, WYETH

Farmakologie: *Equanil* is 2-metiel-2-*n*-propiel-1, 3-propanedioldikarbamaat. *Equanil* werk alleen op die sentrale senuweestelsel in, en het geen regstreekse effek op die spiere, die mioneurale tussenstof of die perifere senuwees nie. *Equanil* blokkeer die intersenuselle eerstens in die thalamus en die stertkern van die subcortex. Dit het feitlik geen effek op die outonoomsenuweestelsel nie, en beweeglikheid van die ingewande, pressor-reaksie en asemhaling word nie geaffekteer nie.

Bobbejane wat met *Equanil* behandel is, het hul gebruiklike vyandige houding teenoor die mens verloor, en vriendelik en mak geword. Hulle behou egter hul belangsteling in hul omgewing, en daar was geen vermindering van hul verstandelike of fisiese bedrywigheid nie.

Toksikologie: Die akute toksisiteit van *Equanil* is besonder laag. Dit skyn asof dit net een-vyfde so toksies soos die meeste barbiturate is. Navorsingswerk wat in verband met subakute en kroniese toksisiteit gedoen is, het geen nadelige fisiologiese of patologiese veranderings aangetoon nie. By die mens het soveel soos 4.8 g. per dag oor 'n tydperk van meer as 6 maande geen toksisiteit tot gevolg gehad nie. Een pasiënt het gedurende 'n tydperk van 15 maande 860 g. gebruik sonder enige nadelige effek.[1] In twee gevalle waar te groot dosisse toegedien is (20 g. en 40 g. onderskeidelik binne minder as 24 uur) is herstel bewerkstellig met behulp van swart koffie en gedurige beweging oor 'n tydperk van 2 uur, opgevolg later deur normale slaap.

Bykomstige Effekte: Geen ernstige bykomstige effekte is gerapporteer nie; af en toe sal 'n pasiënt miskien kla dat hy lomerig voel gedurende die eerste weke van behandeling. Hierdie effek verdwyn dikwels spontaan as die terapie voortgesit word, en kan soms uitgeskakel word deur die dosis te verminder. Verbygaande hoofpyn en maagongerief is genoem, maar geen duiseligheid, mislikheid, braking, diarree of nadelige effek op die funksies van die lewer is gerapporteer nie. Allergiese manifestasies is waargeneem by 3 pasiënte.[1] Die eerste het aan floute-aanvalle en hipertermie (102°F.) begin ly 2½

uur nadat 800 mg. toegedien is, ten gevolge waarvan die terapie gestaak moes word. By die tweede pasiënt is die terapie gestaak omdat angio-edeem sy verskyning na 6 dae gemaak het. Die derde pasiënt het na 4 dae van behandeling aan netelroos begin ly, maar kon voortgaan met die middel toe 'n antihistamien gelyktydig toegedien is.

Voordele: *Equanil* verban besorgdheid; verslap die skeletspiere; en werk sentraal in, maar het geen effek op die werking van die hart, die asemhaling of ander outonoomfunksies nie. Dit het 'n langdurige uitwerking. Kliniese utiliteit word nie deur onwenslike bykomstige effekte aan bande gelê nie. As dit mondeling geneem word, is dit betroubaar en doeltreffend, en veroorsaak geen mislikheid of braking nie.

Indikasies: Besorgdheids- en spanningtoestande; neurologiese toestande waar spiertrekkings 'n faktor is; spiertrekkings wat aan rumatiekagtige toestande te wyte is, sekere stuiptrekkingskwale.

Daar is geen kontra-indikasies vir die gebruik van *Equanil* nie.

Dosis: Gewoonlik 1 tablet t.i.d. *Equanil* word mondeling toegedien in die vorm van tablette van 400 mg. elk. Die aanbevole aanvangsdosis is een tablet drie maal per dag, en, indien die nodige indikasies aanwesig is, 'n addisionele tablet voor slapenstyd. Die dosis kan vermeerder of verminder word ooreenkomstig die kliniese reaksie van die pasiënt. Weens die lae toksisiteit van *Equanil* kan daar maklik in 'n groot verskeidenheid van behoeftes voorsien word.

Beskikbaar: Tablette, 400 mg. elk, bottels van 24.

Versprei ders: Wyeth Laboratories (Pty.) Ltd., Stasiestraat 54, Oos-Londen.

VERWYSING

1. Selling, L. S. (1955): J. Amer. Med. Assoc., **157**, 1594.

IBEROL FILMTABS (ABBOTT)

'n Nuwe, klein, smaaklose tablet is deur Abbott Laboratories ontwikkel vir die behandling van ystergebreke en voedingsanemie.

Die nuwe tablet wat *Iberol Filmtabs* genoem word, is vermoedelik die enigste bloedversterkmiddel van sy grootte wat yster met lewer, plus die volledige B-kompleks en vitamien C, verskaf.

Die begrip wat ten grondslag van die nuwe produk lê, is: ‚Waar 'n ystergebrek vasgestel is, is ander voedingstekortkominge waarskynlik.' Dit is op 'n lyn met die werk van talle ondersoekers wat beter reaksie op ysterterapie verkry het toe hulle die behandling met natuurlike bronne van die vitamien B-kompleks aangevul het. Die Funksie van die B-kompleks is om die voedingstoestand van die pasiënt te verbeter en om te help met die vorming van rooi bloedselle.

Afgesien van sy terapeutiese effek word daar gemeen dat die preparaat 'n nuwe en gerieflike manier is om bloedarmoede te behandel, want die dosis is slegs 2 per dag en die Filmtabs is smaakloos en word maklik ingesluk.

Die 2-per-dag-dosis verskaf 'n optimum-hoeveelheid yster, plus vitamien B_{12} met intrinsieke-faktorkonsentraat, foliensuur, askorbiensuur, lewerfraksie, tiamienmononitraat, riboflavien, nikotinamied, piridoksienhidrochloried en kalsiumpantotenaat.

Iberol Filmtabs is verkrygbaar in bottels van 25 en 100.

PREPARATIONS AND APPLIANCES

CORDEX TABLETS

FOR MILD TO MODERATE RHEUMATIC CONDITIONS

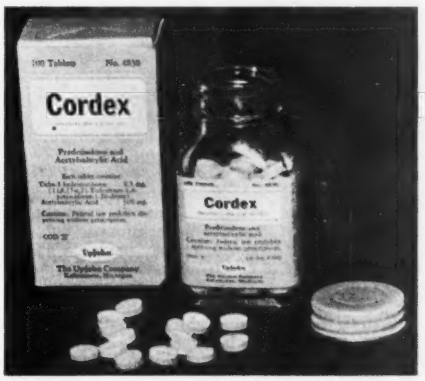
Each tablet contains:

Delta-1-hydrocortisone ... ... (11b, 17a, 21-Trihydroxy-1, 4-pregnadiene-3, 20-dione)	0.5 mg.
Acetylsalicylic Acid	300 mg.

Description: Cordex Tablets combining the anti-inflammatory anti-rheumatic action of delta-1-hydrocortisone with the analgesic action of acetylsalicylic acid, are designed primarily for use in patients with mild to moderate rheumatic conditions.

Indications: Cordex Tablets are indicated in the following conditions when they are of mild to moderate severity and are not controlled by salicylates alone: rheumatoid arthritis, osteoarthritis, gouty arthritis, bursitis, tenosynovitis, myositis, fibrositis and neuritis.

Dosage: The usual dosage is 1 to 2 tablets 4 times daily, with a maximum dosage of 3 tablets 4 times daily. For optimal benefit, particularly in patients likely to require long-term treatment, the starting dose should be based on the patient's tolerance to acetylsalicylic acid. The initial dose should be continued until a satisfactory clinical response is obtained, at which time the dose should



be reduced to a minimal effective level. To minimize the possibility of gastric irritation, each dose should be taken immediately after meals and at bedtime.

The maximum dosage of 3 Cordex Tablets 4 times daily supplies 6 mg. of delta-1-hydrocortisone and the development of undesirable hormonal effects is therefore unlikely. Nevertheless, patients receiving Cordex Tablets should be observed carefully, the same precautions being observed as with other forms of adrenocorticoid therapy.

Packaging: Cordex Tablets are packed in 24's and 100's.

Distributors: Westdene Products (Pty.) Ltd., 22-24 Essanby House, 175 Jeppe St., Johannesburg.

EQUANIL

MEPROBAMATE, WYETH

Pharmacology: *Equanil* is 2-methyl-2-*n*-propyl-1, 3-propanediol dicarbamate. *Equanil* acts on the central nervous system only, and has no direct effect on the muscle, the myoneural junction or peripheral nerves. *Equanil* selectively blocks interneurons primarily in the thalamus and caudate nucleus of the sub-cortex. There is virtually no effect on the autonomic system, and intestinal motility, pressor response and respiration are not affected.

Monkeys treated with *Equanil* lose their customary hostile behaviour toward human beings and become friendly and docile. They retain interest in their surroundings, however, and show no decrease in mental or physical activity.

Toxicology: The acute toxicity of *Equanil* is very low. It appears to be about one-fifth as toxic as most barbiturates. Studies on subacute and chronic toxicity showed no detrimental physiological or pathological changes. In Man, as much as 4.8 g. per day for over 6 months has produced no toxicity. One patient consumed 860 g. over a 15-month period without ill effects.[1] In two cases of overdosage (20 g. and 40 g. respectively, in less than 24 hours), black coffee and constant movement for 2 hours permitted recovery and, subsequently, normal sleep.[1]

Side Effects: Serious side effects have not been reported; an occasional patient, however, will complain of drowsiness during the early weeks of treatment. This effect often subsides spontaneously with continued therapy and can sometimes be eliminated by decreasing the dosage. Transient headache and gastric discomfort have been mentioned, but there are no reports of dizziness, vertigo, nausea, vomiting, diarrhoea or adverse effects on liver function. Allergic manifestations have been reported in 3 patients.[1] The first had fainting and hyperthermia (102°F.) 2½ hours after 800 mg., which necessitated discontinuance of therapy. In a second patient, therapy was stopped because of an angioedema after 6 days. The third patient developed urticaria after 4 days of treatment, but continued on the drug when an antihistamine was administered concurrently.

Advantages: *Equanil* relieves anxiety; relaxes skeletal muscle; acts centrally yet has no effect on heart action, respiration or other autonomic functions; has prolonged action. Clinical utility has not been limited by undesirable side effects. Taken orally, it is reliably effective without causing nausea and vomiting.

Indications: Anxiety and tension states; neurological conditions where muscle spasm is a factor; muscle spasm due to rheumatic conditions; certain convulsive disorders.

There are no contraindications to the use of *Equanil*.

Dosage: Usually one tablet t.i.d. *Equanil* is administered orally in tablets of 400 mg. each. The recommended starting dose is one tablet 3 times a day and, if indicated, an additional tablet an hour before retiring. The dose may be adjusted, either up or down, according to the clinical response of the patient. Because of the low toxicity of *Equanil*, wide variations in need can readily be met.

Supplied: Tablets, 400 mg. each, bottles of 24.

Distributors: Wyeth Laboratories (Pty.) Ltd., 54 Station St., East London.

REFERENCE

1. Selling, L. S. (1955): J. Amer. Med. Assoc., **157**, 1594.

IBEROL FILMTABS (ABBOTT)

A new, small, tasteless tablet has been developed by Abbott Laboratories to treat iron deficiency and nutritional anaemias.

Called *Iberol Filmtab*, the new tablet is reported to be the only haematinic of its size that supplies iron with liver plus the complete B complex and vitamin C.

The concept behind the new product is 'where iron deficiency is established, other nutritional deficiencies are likely'. This follows the thinking of many investigators who have obtained better response to iron therapy by supplementing the treatment with natural sources of the vitamin B complex, the function of the B complex being to improve the nutritional state of the patient and to aid in the formation of red blood cells.

In addition to its therapeutic effect, the preparation is believed to offer new convenience in treating the anaemias because the dosage is only 2 a day and the Filmtabs are tasteless and easily swallowed.

The 2-a-day dosage supplies an optimal amount of iron, plus vitamin B_{12} with intrinsic factor concentrate, folic acid, ascorbic acid, liver fraction, thiamine mononitrate, riboflavin, nicotinamide, pyridoxine hydrochloride and calcium pantothenate.

Iberol Filmtabs are available in bottles of 25 and 100.

DYSPHAGIA

W. L. PHILLIPS, M.R.C.P., LOND., F.R.C.S., ENG.
Cape Town

(*Continued from p.* 329)

SPECIAL INVESTIGATIONS

Special investigations are usually necessary to elucidate the cause of the dysphagia. As the greater part of the digestive tract is not ordinarily visible or palpable, the radiographic examination is most important. Endoscopic inspection may be necessary after the X-ray examination (Fig. 7). I, personally, will only perform an endoscopy after an X-ray examination, which may indicate the site and nature of the lesion. This knowledge is very necessary as it may prevent the examiner from performing a dangerous procedure, e.g. inserting an oesophagoscope into the *cul de sac* of a diverticulum.

1. X-RAY EXAMINATION

The type of radiographic examination will be modified to some extent by the patient's history, e.g. different examinations will be required for cases involving foreign bodies and cases of hiatus hernia. General principles, however, should be followed.

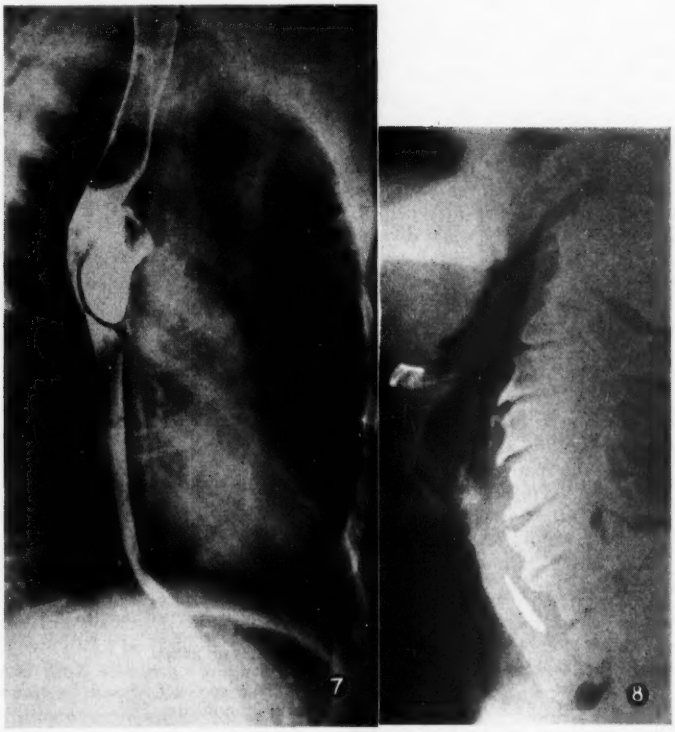


Fig. 7. Traction diverticulum of the mid-oesophagus. The barium-filled oesophagus and diverticulum show that an oesophagoscope would go straight into the diverticulum.
Fig. 8. Exostoses from the cervical vertebrae projecting forwards into the oesophageal region.

(*a*) *Fluoroscopic Examination.* A routine screening of the neck, chest and upper abdomen should always be performed. Straight films should be exposed to show any doubtful area, such as a retrosternal swelling, a thoracic stomach or exostosis of the lower cervical vertebral bodies (Fig. 8).

(*b*) *Barium Swallow.* A thick barium paste should be administered to show up the pharynx down to the stomach; several features must be demonstrated specifically. The examination is essentially a fluoroscopic investigation and films are taken to record the appearances of the oesophagus. This investigation requires skill and experience.

It is important that a preliminary view of the chest should have been obtained, as the dysphagia may be due to some intra-thoracic lesion unconnected with the oesophagus.

The oesophagus must be visualized from the pharynx to the opening in the diaphragm. The speed with which the barium enters through the cricopharyngeus should be noted. The size of the muscular tube and its relationship to the other mediastinal organs must be recorded. The normal indentations due to the aorta, the left bronchus and the left auricle may help to localize a lesion accurately. Abnormal diverticula, strictures, filling defects or ulcer craters may be demonstrated. The emptying rate of the oesophagus is most important and any unusual relationship to the cardiac orifice of the stomach should be observed. The oesophagus may appear shortened or it may be congenitally short.

The presence of the gastric air bubble should be ascertained and, before an oesophagus is considered normal, the patient should have been examined in the Trendelenberg position. The normal oesophageal contraction and the silhouette of the organ should be demonstrated. It is indeed rare for the barium examination of the oesophagus to fail to demonstrate a lesion which is present.

2. BRONCHO-OESOPHAGOSCOPY

The preliminary barium swallow examination will have demonstrated the presence of lesions and their sites. The endoscopist will have been forewarned.

The bronchoscopy should always be performed first, especially if the examination is to be done under general anaesthesia. The anaesthetist will have to intubate the patient before the oesophagoscopy is carried out.

The dysphagia may be due to an oesophageal carcinoma which has involved the left main bronchus. The tumour may have ulcerated through the bronchial mucosa and the bronchoscopy will immediately indicate the inoperability of the condition.

During the passage of the instruments, the pharynx will have been examined for abnormalities in its walls or in its pyriform fossae. Certain anatomical landmarks should be remembered, e.g. in the adult, the cricopharyngeus muscle is situated 16 cm., the aorta 23 cm., the left main bronchus 27 cm. and the hiatus in the diaphragm 38 cm. from the incisors.

The examination should include reports on:

(*a*) The *mucous membrane*—its colour in the whole of its course, the presence of erosion, ulcers, varices, or webs (Fig. 9).

Fig. 9. Oesophageal varices demonstrated by barium and confirmed at oesophagoscopy. The varices show up as negative shadows.

(*b*) The presence of *strictures* and their degree, i.e. complete, partial and length. If a stricture is found it is reasonable to attempt dilatation at the time of examination.

(*c*) Evidence of *tumour tissue* and its site. If possible a specimen should be removed for histological examination.

Perforation of the oesophagus may occur even when all precautions have been taken. It is important that a perforation should be recognized so that immediate treatment can be instituted.

One or two intramuscular injections of penicillin and streptomycin should be given to patients after a biopsy specimen has been taken, as this aids in the prevention of local infection. If a perforation has occurred, or is

suspected, then a post-operative chest film should be taken. All food by mouth should be stopped for the first 24 hours, until the complication has been confirmed or excluded. The prompt use of antibiotics, intravenous infusions and the stopping of food by mouth, have reduced most of the dangers of oesophageal perforation.

TREATMENT OF DYSPHAGIA

1. MAINTENANCE OF NUTRITION

The prime consideration is to ensure an adequate food intake for the patient. In many instances the patient is so emaciated that the prevention of death from starvation is a matter of urgency. In cases of carcinoma of the oesophagus it is surprising that the effects of starvation cannot be overcome by the replacement of food alone. The carcinoma itself apparently has some effect on the metabolism, so that although some improvement can be secured, complete return to normal does not occur. The maintenance of nutrition must be considered in the light of the following facts:

(*a*) The patient may only be able to swallow fluids, and those with difficulty. This means that there is a channel for food to pass, even though it is very narrow. In such cases, if there is no contra-indication to allowing the patient to swallow, a small duodenal or some similar tube may be passed, perhaps after some dilatation of the oesophagus, and highly concentrated fluid foods can then be administered.

(*b*) The patient may be able to swallow with difficulty, but from a surgical point of view it may be undesirable to allow him to do so, e.g. after an injury or manoeuvre the oesophagus may have been perforated and any swallowing may result in a mediastinitis. The same position holds immediately after an oesophageal resection.

In such cases, intravenous feeding is essential until swallowing can be resumed. It must be remembered that all body requirements must be provided; thus fluid, glucose, salt balance and protein requirements should be ensured. Careful attention should be paid to the electrolyte balance and if there is any need for antibiotics these, too, can be supplied intravenously.

(*c*) The palliative use of a gastrostomy or ileostomy is controversial. In my opinion, if the patient requires pre-operative building up and is unable to swallow at all, intravenous alimentation is the method of choice and can be prolonged for as long as 7–10 days. The main indication for either of these 2 operations is in completely inoperable cases where the patient is unable to swallow. The gastrostomy or ileostomy usually proves to be of very temporary assistance as the general deterioration in these cases of inoperable carcinoma is extremely rapid.

2. SURGICAL TREATMENT

The upper alimentary canal may often be restored to normality by operative procedures.

Strictures of non-malignant origin may be dilated at several sessions, and as large a bougie as the oesophagus will permit should be left *in situ*. This passive dilatation is extremely important.

Diverticula can be removed by the one-stage operation with complete safety. A variety of methods has been described, all with some specific merit.

Resection of the oesophagus may be indicated in some of the benign conditions or where permanent damage has been caused by caustic poisons. In such cases procedures such as end-to-end anastomosis or oesophago-gastrostomy, or an intestinal replacement of the oesophagus, may be successfully employed.

The operation of oesophagectomy for carcinoma has an unhappy history. In all centres in the world, oesophagectomy for carcinomas of the upper and middle thirds of the oesophagus carries a very high operative mortality. The operation itself is often difficult, but the post-operative complications seem to be the greater hazard. Lower third carcinoma has a much better prognosis. It may be stated categorically that carcinoma of the upper and middle thirds of the oesophagus carries so high a surgical mortality rate that many surgeons refuse to carry out resection treatment, and prefer to perform 'bypass operations', i.e. the short-circuiting of the carcinomatous site.

The dysphagia due to hiatus herniation can be cured by repair of the hernia. The maintenance of the cardiac sphincter and the sling action of the right crus to the diaphragm are the basic factors to be considered in most repair operations.

Achalasia of the cardia may be overcome by repeated dilatations or they may require a plastic operation of the Heller type.

As in all intrathoracic operations, it is important to remember that post-operative chest drainage provides a safety valve to any leakage from the oesophagus, at the same time allowing of the escape of pleural effusion.

Rapid re-expansion of the lung helps to encourage early healing.

SUMMARY

The etiology of dysphagia is reviewed with special reference to carcinoma of the oesophagus.

Special investigations, diagnosis and treatment are outlined.

X-ray films of cases illustrate some of the many causes of dysphagia.

OPSOMMING

Die etiologie van disfagie word bespreek, met spesiale verwysing na karsinoom van die slukderm.

Spesiale ondersoekingswerk, diagnose en behandeling word kortliks geskets.

X-straal-plate van gevalle illustreer 'n paar van die talle oorsake van disfagie.

AGENESE VAN DIE CORPUS CALLOSUM

M. H. FAINSINGER, M.D., D.M.R.D.

Johannesburg

Gebrekkige ontwikkeling van die corpus callosum is waarskynlik nie so seldsaam as wat die enkele gevalle wat beskryf is in die literatuur, sou wou aandui nie. Die afwesigheid van 'n kenmerkende kliniese beeld is moontlik 'n verklaring vir hierdie klein aantal gevalle. In 1951 het Sheinmel *et al.*[1] die 21ste geval wat radiologies gediagnoseer is, beskryf. Die volgende is blykbaar die 22ste geval.

Omtrent die funksie van die corpus callosum is daar maar min bekend. Dit is egter bekend dat deursnyding daarvan geen stoornis van koordinasie, reflekse, beweging, spraak of van verstand meebring nie. Die oorsaak van gebrekkige ontwikkeling van die corpus callosum, sowel as die formasie van 'n lipoom van die corpus callosum, wat moontlik 'n verwante toestand is, word ook ewe min verstaan. Dit word vermoed dat die toestande voorbeelde is van 'n ‚status dysraphicus'. Ander voorbeelde is spina bifida, miëlocele, voortbestaande metopiese naat, en tregtervormige borskas.

In 'n oorsig van die 21 gevalle wat met behulp van X-strale gediagnoseer is, skryf Sheinmel dat die mees algemene kliniese bevindinge waarom die pasiënte vir verdere ondersoek verwys word, subnormale verstandsvermoë en stuipe is. Die laasgenoemde word gekenmerk deur afwesigheid van 'n konstante patroon en is sonder lokaliseringswaarde.

Davidoff en Dyke[2] meld sewe kenmerke in hulle klassieke beskrywing van die radiologie van agenese en hulle word kortliks as volg herhaal.

1. Die laterale ventrikels is altyd tot 'n mindere of meerdere mate van mekaar geskei.

2. In die sagittale opnames het die dorsale grens van die laterale ventrikels altyd 'n tipiese hoekvormige voorkoms.

3. Die mediale wande van die laterale ventrikels is konveks, en wanneer hulle met lug gevul word om as kontrasmiddel te dien, word die buiging van die mediale wand in die sagittale opnames demonstreer.

4. Die agterste gedeelte van die laterale ventrikels, veral die occipitale cornua, is uitgeset.

5. Die foramina interventriculares van Monro is verleng.

6. Die derde ventrikel is uitgeset en strek na bo heelwat verby sy normale grense. In talle gevalle strek die dak hiervan tot dieselfde hoogte as dié van die laterale ventrikels.

7. Die sulci van die mediale aspekte van die serebrale halfronde vertoon 'n straalvoorkoms rondom die dak van die derde ventrikel en hulle kan bespeur word deur die verwagte posisie van die corpus callosum.

Die differensiële diagnose is in die eerste plek lipoom van die corpus callosum. In seldsame gevalle, kan ander gewasse van die corpus callosum, of aangebore kistes van die septum pellucidum, daarmee verwar word. Ander massas in die gebied, b.v. gewasse van die septum pellucidum, van die mediale wande van die laterale ventrikels, van die derde ventrikel, of middellyn meningiome kom net tot 'n geringe mate daarmee ooreen en met bogemelde kenmerke as basis, is dit maklik te onderskei.

Wat lipoom van die corpus callosum betref, is die waardevolste onderskeidingspunte te vind in die roetine opnames van die skedel. Verkalking van die omlyning van die lipoom self en vermeerderde deurskynendheid weens die hoë vet inhoud, is dikwels te bespeur.

Van bogemelde kenmerke is die gebruiklikste onderskeidingsteken verhoging van die

derde ventrikel. Van 14 gevalle wat deur Bunts en Chaffee[3] nagegaan is, was dit in 12 aanwesig. Verdere verskilpunte is die verlenging van die interventrikulêre foramina en die hoekvormige dorsale grense van die laterale ventrikels met agenese. Die laasgenoemde 3 kenmerke is verantwoordelik vir die sogenaamde „vlermuis vlerk' voorkoms.

Wanneer daar 'n groot cavum septi pellucidi bestaan wat met die derde ventrikel verbind is, mag daar verwarring ontstaan tussen die skaduwee van die cavum en 'n verhoogde derde ventrikel. Met voldoende lugvulling behoort die aparte skaduwees van die cavum en die derde ventrikel, met hulle kenmerkende vorms, opmerkbaar te wees en onder dié omstandighede kan agenese van die corpus callosum uitgeskakel word.

Met 'n cavum septi pellucidi wat nie met die derde ventrikel verbind is nie, d.w.s. 'n kiste van die septum pellucidum, sal daar geen verwarrende lugskaduwees tussen die laterale ventrikels wees nie en die onderskeiding is eenvouding.

VERSLAG OOR 'N GEVAL

'n Blanke vroulike baba van 18 maande het vanaf geboorte stuipe gekry. Hulle het erger geword alhoewel hulle nie meer dikwels voorgekom het nie. Hulle het geen plaaslike letsel aangedui nie en was van nie-spesifieke aard. Die ontwikkeling van die baba was vir haar ouderdom waarskynlik ietwat vertraag. Die familie geskiedenis het niks belangriks getoon nie.

Lug-enkefalografie (Fig. 1-4) is toe deur lumbale punksie uitgevoer en 'n diagnose van agenese van die corpus callosum is gestel.

Met operasie is geen teken van die corpus callosum gevind nie. Die derde ventrikel is

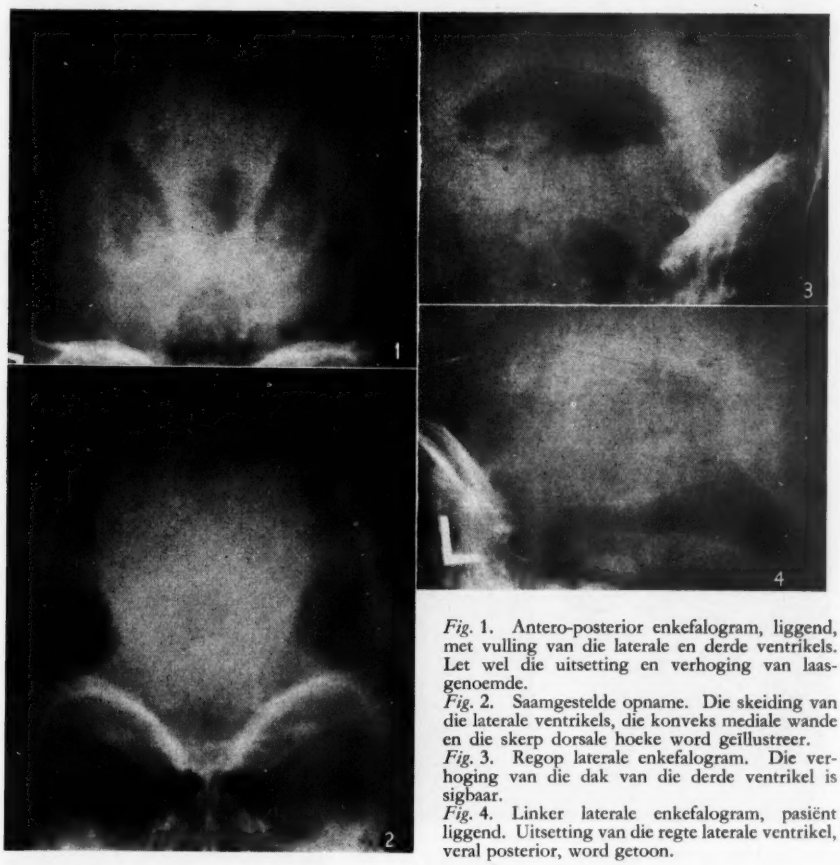


Fig. 1. Antero-posterior enkefalogram, liggend, met vulling van die laterale en derde ventrikels. Let wel die uitsetting en verhoging van laasgenoemde.
Fig. 2. Saamgestelde opname. Die skeiding van die laterale ventrikels, die konveks mediale wande en die skerp dorsale hoeke word geïllustreer.
Fig. 3. Regop laterale enkefalogram. Die verhoging van die dak van die derde ventrikel is sigbaar.
Fig. 4. Linker laterale enkefalogram, pasiënt liggend. Uitsetting van die regte laterale ventrikel, veral posterior, word getoon.

van bo oopgemaak en uitsetting daarvan is vertoon. 'n Fistel is tussen die ventrikel en die sub-arachnoïde spasie gemaak.

Na operasie het die pasiënt spoedig herstel maar daar is dusver geen opvolgstudie gemaak nie.

OPSOMMING

Die 22ste geval van agenese van die corpus callosum deur radiologiese metodes gediagnoseer word beskryf en die kenmerke sowel as differensiële diagnose word kortliks nagegaan.

SUMMARY

The twenty-second case of agenesis of the corpus callosum diagnosed radiologically is described.

The characteristic features as well as the differential diagnosis of the condition are briefly reviewed.

Ek erken graag die hulp van Dr. David Gamsu wat die geval na my verwys het.

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SKELETAL CHANGES IN ENDOCRINE AND METABOLIC DISORDERS

X. ACROMEGALY

W. P. U. JACKSON, M.D.
Department of Medicine, University of Cape Town, Medical School, Mowbray, C.P.

The clinical features of this condition are too well known to need description. It seems plain that the basic lesion is a functioning adenoma of the eosinophil cells of the anterior pituitary which produces too much growth hormone. On the other hand, an excess of circulating growth hormone cannot yet be satisfactorily demonstrated by any test. A raised serum inorganic phosphorus is believed to be evidence of its action and is used as a test of continued growth and activity of the tumour.

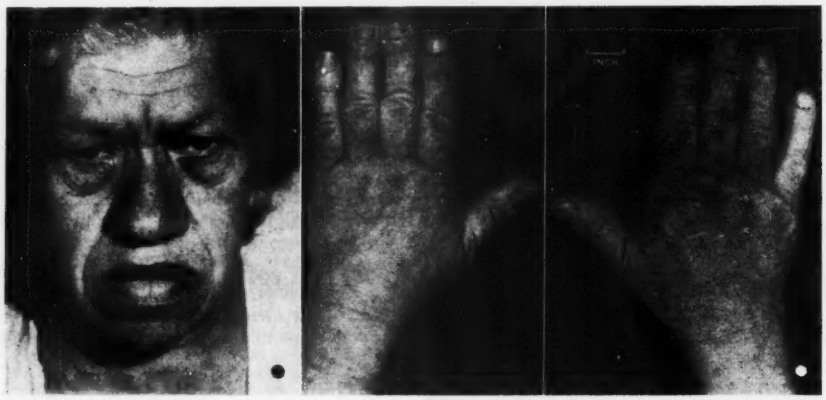

Fig. 1. Typical acromegalic facies: large nose, large lips, coarse heavily wrinkled skin. (Dr. C. Merskey's case, to whom acknowledgement is made).
Fig. 2. Hands of the same patient.

Figs. 1-5 illustrate the condition.

The *skeletal changes* may be described under 5 main headings:

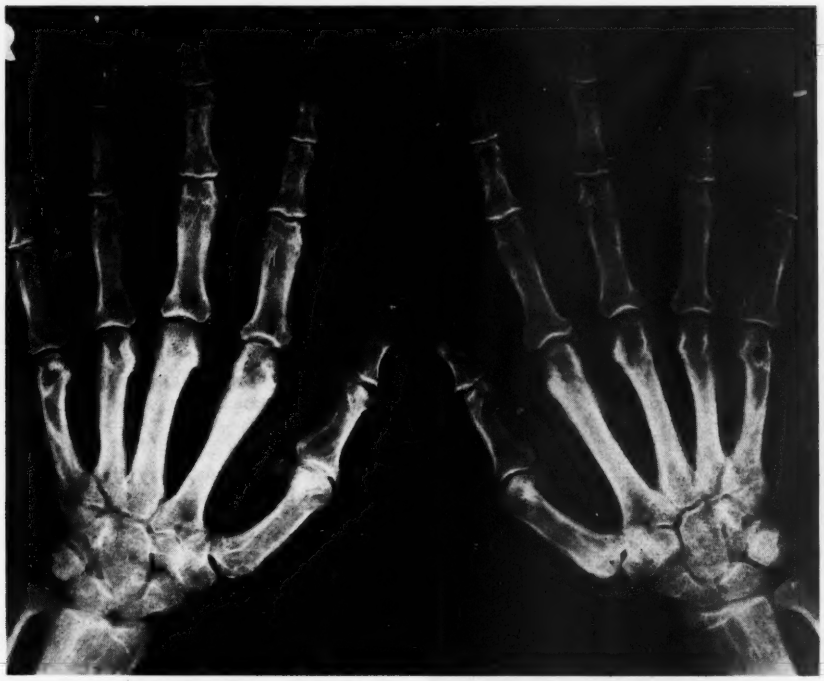

Fig. 3. X-ray of the hands show:
1. Pronounced tufting of finger ends;
2. Periosteal overgrowth at tendinous attachments;
3. Coarse trabeculation and probable porosis.

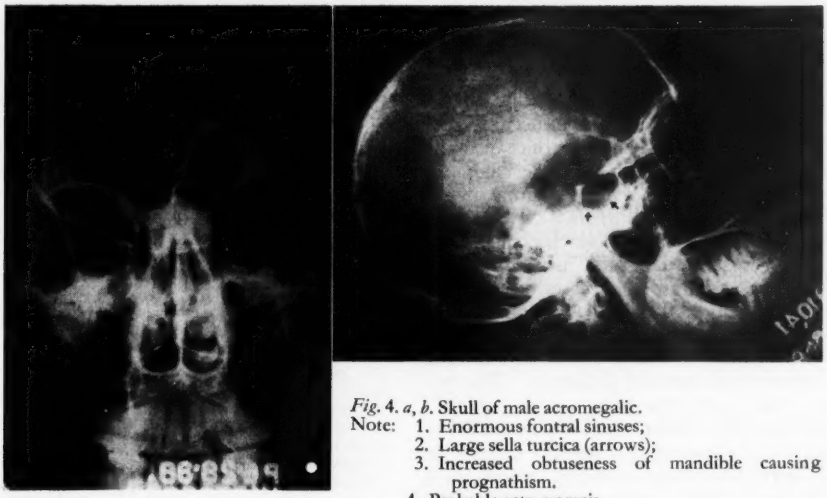

Fig. 4. *a, b.* Skull of male acromegalic.
Note:
1. Enormous fontral sinuses;
2. Large sella turcica (arrows);
3. Increased obtuseness of mandible causing prognathism.
4. Probable osteoporosis.

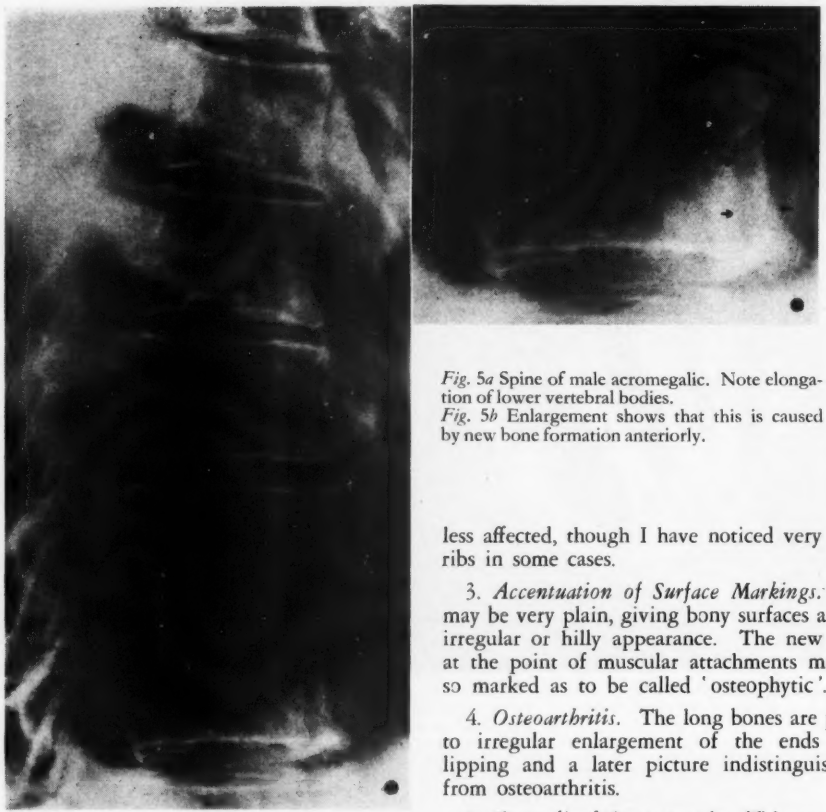

Fig. 5*a* Spine of male acromegalic. Note elongation of lower vertebral bodies.
Fig. 5*b* Enlargement shows that this is caused by new bone formation anteriorly.

1. *Growth in Length of Bone.* This is, of course, the cause of gigantism if the pituitary hyperfunction is active before closure of the epiphyses. In the adult it cannot occur, except in the mandible, which becomes thickened and lengthened, its angle more obtuse, the arch enlarged and the symphysis prognathic.

2. *Growth in Width of Bone.* Periosteal new bone formation accounts for this. The skull is generally thickened, particularly the cheek bones. The frontal sinuses are enlarged and the supraorbital ridges prominent. The bones of the hands and feet are thickened, with an increase in size of the normal tufts at the ends of the terminal phalanges. The vertebrae may gain new bone on the anterior surfaces of their bodies, especially in the lower dorsal region, leading to a marked increase in their horizontal diameter when viewed in a lateral radiograph. Other bones are usually less affected, though I have noticed very thick ribs in some cases.

3. *Accentuation of Surface Markings.* This may be very plain, giving bony surfaces a most irregular or hilly appearance. The new bone at the point of muscular attachments may be so marked as to be called 'osteophytic'.

4. *Osteoarthritis.* The long bones are prone to irregular enlargement of the ends with lipping and a later picture indistinguishable from osteoarthritis.

5. *Generalized Osteoporosis.* This may lead to irregular collapse of vertebral bodies. Most acromegalics in the active phase are in negative calcium balance with a high urine calcium output, despite their tendency to a positive retention of nitrogen. The cause of osteoporosis in acromegaly is unknown. Albright favours hypogonadism secondary to pituitary disease as the cause, but the follicle stimulating hormone assay is not always low.

OPSOMMING

Die skeletveranderings ten gevolge van akromegalie word uiteengesit en geïllustreer.

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SMOKING AND LUNG CANCER

A STATISTICAL STUDY OF ITS ASSOCIATION*

JOSEPH BERKSON, M.D.

Section of Biometry and Medical Statistics, Mayo Clinic, Rochester, Minn., U.S.A.

'In a very real sense the excellence of a person as a statistician may be said to depend largely upon his native ability by some obscure sixth sense to avoid the fallacy of observational selection.' Edwin B. Wilson.[1]

When I encountered the first of the series of statistical studies on the association between smoking and lung cancer which have recently appeared,[2, 3] it immediately recalled to me a prior investigation on the association between tuberculosis and cancer.[4] My thinking on the present question has developed out of careful study which I had made of the older work. I shall take the liberty of elaborating my analysis by way of reference to that investigation as a base, not only because in the circumstances it is natural for me to do so, but also because I believe it will be instructive.

The investigation referred to was founded on an observation, first made by the renowned pathologist Rokitansky and noted also by others, that tuberculosis and cancer occurring together in the same individual appeared to be very rare. A study was instituted using the records of the Pathological Laboratory of the Johns Hopkins Hospital. The records of 816 cases were isolated in which at necropsy some form of malignant neoplasm had been found. The question was, in the words of the author:

'To what extent, in point of frequency, was tuberculosis, active or healed, associated with the presence of malignant neoplasms in the 816 cases of malignancy comprised in this autopsy material? Were tuberculosis lesions, active or healed, found at autopsy more or less frequently in this group of 816 cases of malignant neoplasms, than such lesions would be expected to be found in an equal number of non-cancerous persons, of the same ages, sexes, and races as the 816 persons composing the cancerous group?'

To answer this question a control group of necropsied persons was set up with which the cancerous group could be compared, in the following manner: The entire set of records pertaining to non-cancerous persons, that is the whole of the body of cards carrying the necropsy records minus the 816 cards comprising the cancerous group, were arranged in order of date of necropsy, and similarly the 816 cards of the malignancy group were arranged in order of date of necropsy.* Starting with the earliest card in the cancerous group, the first card in the non-cancerous group was found which corresponded in respect to race (coloured or white), sex and age, and similarly corresponding cards in the non-cancerous group were found for the second and succeeding cards in the 816 of the malignancy group. As the author expressed it:

'The final outcome of this procedure was to give 816 cards pertaining to persons who had no malignant tumours at death, but who had, as a group, precisely the same sex, colour and age distribution as the 816 persons, taken as a group, who did have malignant tumours at death. Furthermore each person in the control group died at about the same date as his cancerous partner in the group of malignant cases . . . the control group is selected to agree in one-to-one correspondence with the malignant group in respect of sex, colour, age, and date of death . . . But the composition of the group is completely random in respect of pathological lesions, save for the fact that it contains no case of malignant neoplasm.'

The whole weight of the presentation is placed on the presence of a control. At various points in the article the author takes up the possible unrepresentative character of the data as a whole in one or another respect, but always this is met with the argument that the controls as well as the malignancy group are equally unrepresentative. Thus there is some discussion of the possibility that the percentages of tuberculous lesions are perhaps comparatively low both in the malignancy and in the control group. The author points out that the number of cases in which any lesion is found indicating the presence of tuberculosis depends on the zeal with which the search for such lesions is conducted. As respects this he says:

'From the point of view of the present study the

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* For brevity I am presenting only the essential elements of the procedure, not necessarily the actual details of how it was carried out.

question of the meticulousness of the search for minute healed lesions of tuberculosis has no relevance. The logical procedure in this study has been throughout to compare specifically diseased (malignancy) and control groups. The procedure of the pathologists in looking for and recording tuberculous lesions, active or healed, has been uniform in both groups . . . Only if it were differential could the absolute number of tuberculous lesions found be significant in the present study.'

I have quoted somewhat extensively from the author, to make clear a particular point which it is important for me to establish. Note how analytically careful the author is, how he stresses the importance of a properly constituted control, how he rests his case on the establishment of such a control and how he finally summarizes the objective attained. What Pearl has done here is a paradigm of what, according to widely held opinion, are the essentials for a perfectly performed experiment of statistical comparison. He takes two samples from the identically same population, at random otherwise than that they have been stratified to be comparable in every relevant respect except one, namely that in the one group each individual has a malignant neoplasm, and in the other no individual has a malignant neoplasm. Then he is to compare the two groups in respect of tuberculosis, and if a material difference is found—so the argument goes—what can it be attributed to except that there is some association between cancer and tuberculosis?

What then were the findings as respects tuberculosis in the two groups? The answer is that active tuberculosis was found in only 6.6% of the 816 persons having malignant tumours and in 16.3% of the 816 persons without malignant tumours but of the same race, sex and age as the former group; active tuberculosis occurred more than twice as frequently in the controls as it did in the malignancy group. When the data were segregated into sub-groups it was revealed, in the words of the author,

' . . . with the utmost clarity and precision, that in each decade of age, and in each sex and race division of the material, the percentage of persons showing active tuberculous lesions at autopsy is markedly higher in the control group than in the malignancy group.'

The meticulous analyst, having conclusively shown that tuberculous lesions were less frequent among the cases with malignant tumours than among cases without malignant tumours, says that something else should be looked into. He poses the converse question to that first considered: Are malignant tumours more or less frequent among those with active tuberculous lesions at necropsy than they are among those with no tuberculous lesions at necropsy? After a pertinent analysis he concludes:

' The answer is precise and unequivocal so far as concerns the 1,632 autopsies here studied. In each decade of age, over the whole life span, cancer or other malignant tumours occur less frequently in those with active tuberculosis, than in either the non-tuberculous or those with old healed lesions.'

The apparently unequivocal conclusion from the study, that tuberculosis and cancer are biologically antagonistic, was accepted with utmost seriousness. An experiment with animals was set up and an extensive programme of treating cancer patients with tuberculin was instituted.

Now I shall quickly come to the first anticlimax of the story. Even before the definitive publication of the study, objections were advanced as to the validity of the comparison which had been made. So far as I know and understand, although the critical arguments took different specific forms, essentially they had to do with one central point. Since the comparison was of concomitant lesions found at death, consideration had to be given to the duration of the diseases in question, for an individual had to live long enough with one disease to contract the other if the presence of both was to be found at necropsy. These objections were more intensely discussed after the publication, and as a result of these and perhaps also on the basis of evidence that appeared from experiments, on which Pearl always laid the greatest stress,[5] the author was convinced that the original conclusion was doubtful and he issued what amounted to a retraction, from which I shall briefly quote.[6a]

' [A possible interpretation] is that the result is purely fortuitous, the infrequency of association arising from the assumed fact that the time relations of the disease between onset and death are such as to make impossible the complete freedom of joint association which is an implicit postulate of the simple probability theory. Or putting the point less formally, it can be alleged that the reason why persons with cancer are clinically found to have florid tuberculosis less frequently than persons without cancer . . . is because the cancer kills them before there is time for florid tuberculosis to develop.'

Although retrospectively I agree that the conclusion reached by Pearl in his first investigation is not correct and that some *ad hoc* criticisms of it which were expressed have force, still, on the basis of very generally accepted principles of statistical procedure it seems to me that he was invulnerably right. If in 2 'cohorts' of a population, differentiated in respect of only one relevant characteristic x, the finding of an unquestionable difference between the 2, in the relative frequencies of a character y, establishes association between x and y, irrespective of the

character of the population itself, then Pearl's investigation did establish negative association between cancer and tuberculosis and in fact it was an impeccable example of such a demonstration. It is on the validity of this general principle that the most frequently quoted studies on smoking and cancer rest the conclusion that there is an association between smoking and cancer of the lungs.* If on the other hand the population itself must meet some particular criteria, then I submit that no studies have been made directed at discovering just what these criteria must be, still less have they been definitely set down. I have my own idea, but I recognize that it is a personal opinion, without general statistical authority.

My own idea is that, if an essential biologic association is to be established as a definitive scientific conclusion, that is to say, if it is to be considered '*proved*' the population must not be anything else except an *experimental population.* An association found in a purely statistical investigation made on an existent population, by which I mean an investigation which is retrospective as regards either of the variables concerned, however strongly it may suggest association as a *presumptive* conclusion, is tentative until it is corroborated fully by means of experiment. I am not here referring to 'association' in a purely statistical, descriptive sense. If proper study of a given population shows that there is positive correlation between stature and weight, then it is a descriptive fact that tall individuals in that population are on the average heavier than short individuals. But there is no concluding even here that there is a necessary biologic relation between stature and weight; we do not know for instance that the correlation would exist if the population were placed on a different diet. Here I am only restating what Pearl himself asserted:[6a]

'Perhaps in the long run it will appear that the chief usefulness of the statistical technique in methodology of science is the not unimportant one of suggesting problems and lines of attack upon problems which must finally be solved, if they ever are solved, by the application of the methods of experiment and observation, or a close and integrated correlation of these methods with the statistical to reach a common end.'†

And now I conclude briefly in an autobiographical vein with my analysis of Pearl's study. At the time the study was made I thought the logical development on which it was planned was cogent, and when the critical argument was presented on which Pearl's retraction is based, I thought *that* was cogent. But I later came to doubt this also! The particular criticism made was centrally based on the fact that the population concerned was a population of the dead; it was death from cancer that prevented later contraction of tuberculosis, otherwise the tuberculosis would have been found with its representative frequency—that was the argument. I resolved never to study association of diseases in a dead population.

Several years after the events referred to—in the early thirties—I found myself in the position of statistical consultant in a large medical institution. I was amazed at how soon after I took up my duties, and with what frequent recurrence, I was asked questions referring to association between diseases. I believe it was in 1935 that the particular event occurred which I wish to relate. A physician came to me with an idea with which I had

* Pearl's set up fully complies with the requirements laid down by Cutler,[2] who, commenting on some published studies showing association between smoking and cancer, says: 'The sampling techniques used in these case history studies were generally not sophisticated. It may be that the lung cancer cases studied were not representative of all persons with lung cancer and that the controls were not representative of the general population, but these two requirements are not essential. To study the relationship between smoking and lung cancer it is sufficient that the lung cancer cases and controls be drawn from the same population.'

† Another quotation from Pearl[4] (1929) is pertinent to the subject under present discussion: '. . . it is of interest to note that as the frequency of the incidence of fatal tuberculosis of the lungs has declined in recent years there has occurred a marked increase in lung cancer, which has been so notable as to attract the attention of pathologists generally.'

In considering the significance of the putatively real increase of the rate at which lung cancer is developing in the population, Cutler[2] says: 'This increase cannot reasonably be attributed to genetic change in the human population and therefore must be due to environmental factors.' It is not obvious why it *must* be. Individuals reaching the adult cancer ages in current times are, in respect to their constitutional resistance to disease, greatly different from individuals formerly attaining these ages. The marked lowering of death rates in the early ages of life that characterizes the hygiene of the present era has resulted in having in the adult population individuals who in former years would have died in infancy or youth. It is likely that they carry with them a measure of the lower resistance to disease which was the constitutional basis of their former early death. Frost,[6b] in a beautiful and important paper, has shown how high mortality from tuberculosis in later life is related to *escape* from excessive mortality in earlier life. This effect undoubtedly is present with other diseases and especially with disease of the same tissue resistance. It is entirely possible and even likely that at least part of the increase in death rate from lung cancer which has been recently noted is attributable to deaths in adulthood from this disease of individuals who have not been eliminated, as in former years they would have been, by death in early life from tuberculosis or some pulmonary malady.

by now become generally familiar. He said that he had the impression that cancer of the stomach occurred rarely in persons who had duodenal ulcer, and suggested that we might study the pathologic records statistically to check on the validity of his impression. In this particular instance, after I recited the difficulty about working with a dead population, I suggested that we might make the statistical study using the clinical diagnoses made on examination of living patients, of which we had a very complete cross-index file. It was while working out a numerical example, in which I began with a hypothetical general population in which there was not any association but only random frequencies, that I became conscious of a difficulty that prompted me to review the elementary factors that enter into the comparison by which association is established. I reached the conclusion that there is a fallacy in studying association of diseases in the living as well as the dead clientele of a hospital population, and that basically it was on this fallacy that Pearl's investigation of an association between tuberculosis and cancer had foundered.

Thereafter, when association of diseases was broached as a subject for possible investigation, I presented the possibly fallacious character of the conclusion that could be reached if hospital populations, dead or living, were taken as a base. As I mentioned before, the suggestion of association between diseases was periodic and my lecture on the subject became routine. In 1946 my recital impressed one of my hearers and I was urged to publish the analysis. It happened that the case presented referred to a possible positive association between diabetes and cholecystitis, and it was in terms of this example, which was of then current interest, that I did publish it,[7] but what I had in my mind was tuberculosis and cancer. The point of my analysis in detail can be studied in this article. For the moment it will suffice to say that, if the sub-population of the hospital which is used for the comparison of the incidence of a disease y in a group x and its control not-x is not representative in the ratio of the marginal totals of x and not-x of the corresponding ratio in the general population, then, except under special circumstances, association will appear in the hospital population even if none exists in the general population from which the hospital population is drawn.

Although my article[7] has been referred to in the literature on cancer and smoking as possibly relevant in evaluating those studies referred to as 'retrospective', in which patients in a hospital having lung cancer were compared in respect of incidence of smoking with a control group from the hospital not having lung cancer, it has not been cited so far as I know, in connection with the prospective studies which have been published, in which individuals differentiated initially as regards smoking and not smoking are followed to ascertain the relative rate of death from cancer. It was Professor Donald Mainland[8a, b] who suggested to me rather pointedly what I had thought of only vaguely—that it *might* apply also to the prospective studies. We may think of the population sampled in these studies as replacing the hospital population, so far as it is not the entire reference population in which the study of association is the real objective but only a sample of it. In the prospective study of Doll and Hill,[9] for instance, the population actually composing the material of comparison is only a certain portion of the physicians registered at the time of inception of the study and these are only a portion of the general population. In the prospective study of Hammond and Horn[10] the population concerned in the analysis is an unknown fraction of the potential of solicited friends of member workers of the American Cancer Society who answered the questionnaire addressed to them respecting their smoking habits. On more serious consideration than I had first given the idea, it suggested itself to me that a simple mechanism may be operating which will produce spurious association in the selected population similar to that referred to in the study of association of diseases in a hospital population. An artificially simple example of such an effect is the following:

Suppose there is some reference population which we wish to study in order to ascertain whether there is association between smoking and death rate. We will suppose that in this population there is in fact no association, but that this is unknown to us. We visualize the reference population as composed of two groups:

Group I: This is the element of the population which at the time of the beginning of the study is in various degrees of serious ill health; for the most part these individuals are destined to die within a year. If the symptoms of an individual in this group are sufficiently prominent, such an individual may eliminate himself or be eliminated from the investigation deliberately or tacitly by the investigator. It is assumed that an individual

belonging to this group is eliminated or not eliminated from the investigation entirely on the basis of the condition of his health, and quite independently of whether he is or is not a smoker. That is, for this group of individuals with ill health, health is, so to speak, dominant over any other factor that may in general affect whether an individual is selected for the investigated population. We will postulate for a hypothetical example that group I comprises 3% of the reference population, that the death rate in the year for this group is 99% and that only 50% of group I are recruited into the investigation.

Group II: This is the remaining portion of the reference population and the individuals comprising it are free of serious ill health, in the sense that no individual in this group is experiencing symptoms which could be the basis of his elimination from the investigation. Some few members of this group do die during the year from diseases which at the time of the survey were not exhibiting prodromal symptoms, and arbitrarily we set the death rate for this group in the example at 0.03%. In this group II, we assume, whether an individual comes into the investigation or not depends solely on whether he is a smoker, and we will assume that there is a greater tendency for a smoker to eliminate himself than for a non-smoker to do so. Of the non-smokers in this group, we will say that 99% respond, while of the smokers in this group only 65% respond and are included in the investigation.

We consider a reference population of which 80% are smokers and in which the over-all mortality rate for the year is 3%. For this population there is given in table 1, A and B respectively, the constitution of the reference population and that of the selected population. A summary of the comparison is given in table 2.

It is to be observed that while there is no association between smoking and death rate in the original reference population, an appreciable positive association appears in the selected population, the death rate for smokers being 2.3%, while that for the non-smokers is 1.6%. The origin of the appearance in the hypothetical table of spurious correlation, it should be noted, is not a supposed tendency operating directly for an individual to eliminate himself for reasons of ill health with greater probability if he is a smoker than if he is a non-smoker; the individuals who eliminate themselves for reasons of ill health are randomly taken from the population so

TABLE I: STATISTICAL ASSOCIATION PRODUCED BY INTERACTION OF COMPETITIVE RISKS OF SELECTION: HYPOTHETICAL CASE.

A—Reference population, cohort of 100,000

	Exposed			*Deaths*			
Smoker	I	II	*Total*	I	II	*Total*	*Rate per cent*
No. ..	600	19,400	20,000	594	6	600	3·0
Yes ..	2,400	77,600	80,000	2,376	24	2,400	3·0
Total ..	3,000	97,000	100,000	2,970	30	3,000	3·0

B—Selected population, expected number

	Exposed			*Deaths*			
Smoker	I*	II	*Total*	I	II	*Total*	*Rate per cent*
No ..	300	19,206†	19,506	297	6	303	1·6
Yes ..	1,200	50,440‡	51,640	1,188	16	1,204	2·3
Total ..	1,500	69,646	71,146	1,485	22	1,507	2·1

* Of group I individuals (the ill) in the reference population, 50 per cent are recruited, independent of whether they are smokers.

† Of group II's 19,400 non-smokers, 99 per cent are recruited.

‡ Of group II's 77,600 smokers, 65 per cent are recruited.

TABLE II: SUMMARY OF COMPARISON, REFERENCE AND SELECTED POPULATIONS, FROM TABLE I.

	Reference Population, per cent	*Selected Population, per cent*
Proportion of reference population	100	71
Proportion of smokers ..	80	73
Death rate, over-all	3·0	2·1
Among non-smokers ..	3·0	1·6
Among smokers ..	3·0	2·3

far as smoking is concerned. Rather it is the simultaneous operation at different intensities of the selection on both smoking and deaths. I do not mean that it is solely by exactly this mechanism that selection can produce spurious correlation in prospective studies. It is only a 'statistical model', and has been presented because wide acceptance of the prospective studies as probative appears to be based on the idea that with this method of investigation no fallacy is possible. More broadly considered, wherever it is found that selection is operating, it is gratuitous to *assume* that selection does not affect differentially different strata of the population sampled, and therefore one must be prepared to find differences between corresponding strata in the sample, even if there are none in the original population.

The earmark of selection is the appearance in the selected table of an unrepresentative proportionality in the constituents of the marginal totals. In the hypothetical case represented in the table we see that the proportion of smokers is smaller in the selected population than it is in the parent reference population and that also the proportion of deaths is smaller. How do these matters stand in the data of the American Cancer Society study of Hammond and Horn,[10]* from which these authors have concluded that an association between smoking and cancer of the lungs has been *proved,* an association which they attribute to a positive causal relationship? Since cigarette smoking is most clearly indicted in their study, pipe and cigar smoking being less if at all involved, and also because statistics on cigarette smoking are more easy to come by, I shall concern myself only with this form of smoking.

In the study of Hammond and Horn, data are available for current cigarette smokers and also for men who ever were cigarette smokers in their lives. In table 3 are given percentages representing the prevalence of cigarette smoking among males comprising the population of the study of Hammond and Horn, as extracted from their data. For males in the decade of age 50 through 59 years the prevalence of current cigarette smokers is 48.5% * In contrast with this a Gallup poll[11] for June 1954 gives as a national average 57% for current cigarette smokers among males in this age group.† In the total population of the Amrican Cancer Society study, which is composed of white males in the age range 50 through 69 years, the proportion of current cigarette smokers is 42.8%. Surveys referring to all males for various localities in the United States show a median of from 60 to 65% (these, however, must be presumed to refer on the average to younger men than represented in the study from the American Cancer Society). The proportion of men in the American Cancer Society study who reported themselves as having been cigarette smokers at some time in their lives is 57.4%. As against this, the Bureau of Research In-

TABLE III: CIGARETTE SMOKING: DATA OF THE AMERICAN CANCER SOCIETY STUDY[10]

Age, Years	*Percentage*	
	Current Cigarette Smoker	*Cigarette Smoker Some Time in Life*
50–54	51·7	66·6
55–59	45·0	60·5
60·64	37·0	51·6
65–69	28·0	40·7
Summary Totals		
50–59	48·5	
50–69	42·8	57·4

* This study is chosen as the one to examine because it is a prospective study where competitive selection hitherto has been thought not to be relevant, because it provides the most detailed findings of any article published to date, particularly as respects age-specific death rates and because it is the one from which the most definite conclusions have been drawn.

* Calculated by dividing the number given in the study as currently smoking cigarettes (their table 5) by the total number in the corresponding age group (their table 3).

† This poll excluded from the count of cigarette smokers any individuals who were also cigar or pipe smokers; the percentage of 57 is therefore to be considered an under-estimate of current cigarette smoking in this age group of males, in the sense in which it is represented in the quoted statistics of the study of Hammond and Horn.

formation estimates that for the general population this figure is about 75%.[11] Although statistics for exact comparisons are not available, it appears to me that there is little doubt, on the basis of what has been noted, that in the response to the call of the workers of the American Cancer Society for volunteers to enter the projected survey on smoking and cancer there was a 'tendency' for cigarette smokers not to enter themselves, with the result that the sampled population is 'selected', that is unrepresentatively weighted with non-smokers of cigarettes.

Now we will consider the other variable concerned, deaths. For this purpose I have assembled in table 4 a comparison of the death rates in the population of the American Cancer Society study, calculated on an annual basis, and those for United States white males for 1952, which are the latest rates available in the detail required. This table gives a comparison for deaths from all causes and also for specific causes so far as these can be evaluated from the data reported in the publication of Hammond and Horn. It is seen that, without exception, the age-specific death rate from all causes, and from each specific cause, is materially lower for the population of the American Cancer Society study than it is for the corresponding white male population of the United States. I have included in the tabulation the death rates of the non-smokers of cigarettes of the American Cancer Society study. These death rates are seen to be strikingly low compared with those of the United States white male population. The non-smokers of cigarettes in the population of the American Cancer Society study are evidently a lot of phenomenally hardy men. One may reasonably conclude from these comparisons that in the response to the call for individuals to enter the survey, men in relatively poor health tended to be excluded, so that the investigated population is selected favourably as respects death rate from all causes, and from specific causes including deaths from cancer.

Thus the data of the American Cancer Society study taken as a whole exhibit *prima facie* evidence that they have been subjected to a kind of selection which can produce association in the data studied, such as in fact was found in these data, even if the association does not exist in the primary reference population.

The authors of the study themselves appear to be conscious of the fact that selection in their data may be operating which can produce an artificial appearance of association. In the course of describing their procedure they say:

'In planning the study, we had anticipated that deaths that occurred during the first few months would have to be excluded from the analysis in order to avoid the theoretical possibility of a bias influencing the relationship between death rates and smoking habits. In order to test for this, we have made an analysis separately for deaths that occurred in each of three six month periods as well as . . . prior to May. In all four periods, regular cigarette smokers had higher death rates than men who had never smoked. Because of this finding, it was decided to base the present report on all deaths . . . As a matter of fact, the relationships between cigarette smoking and death rates were greater in the last two 6 month periods than in the earlier periods.'

I do not believe that in the last part of the quoted passages the authors meant to imply that cigarette smoking, as a direct or mediate cause of death, was increasing in severity over the several months reviewed. It appears rather that their observations provide pointed evidence that artificial selective factors were operating in the study which could effect an

TABLE IV: COMPARISON OF DEATH RATES FOR THE UNITED STATES WITH THOSE IN THE AMERICAN CANCER SOCIETY STUDY *

	Death Rate, per 100,000 per Year														
	All Causes			*Cancer, Lungs*			*Other Cancer*			*Coronary Heart Disease*			*Other Diseases*		
		A.C.S.			*A.C.S.*			*A.C.S.*			*A.C.S.*			*A.C.S.*	
Age, Years	*U.S. White Males*	*Total*	*Non-Cigarette Smokers*	*U.S. White Males*	*Total*	*Non-Cigarette Smokers*	*U.S. White Males*	*Total*	*Non-Cigarette Smokers*	*U.S. White Males*	*Total*	*Non-Cigarette Smokers*	*U.S. White Males*	*Total*	*Non-Cigarette Smokers*
50–54	1,206	838	602	50	32	6	148	100	91	426	371	230	582	335	274
55–59	1,891	1,345	1,072	85	61	19	259	178	158	701	614	440	846	491	454
60–64	2,793	1,925	1,444	114	56	6	406	298	225	1,018	851	592	1,255	719	622
65–69	4,089	2,905	2,662	127	79	45	609	416	358	1,438	1,247	1,115	1,915	1,163	1,144

* The annual death rates for the population of the American Cancer Society Study were calculated by assuming a uniform exposure of 20 months (median) for all individuals in that population. The rates for United States white males are for 1952 obtained from reference 12 supplemented by a special tabulation referring to deaths from lung cancer for which I am indebted to Mr. I. M. Moriyama.

apparent association between cigarette smoking and death rate. Whatever were the unknown selective forces which caused the relationship of smoking and death rate to appear to be increasing in the last two 6-month periods, these factors were presumably operating also at the beginning of the investigation. If they could bring about an apparent increase of association, it is possible that they may be responsible for the appearance of an association in the first instance, and that what is exhibited in the findings of the study is an elaboration of the detailed effects of this selection. The fact that the exact mechanism of such selective association is not readily visualized is not an adequate reason for considering the suggestion of its possible existence to be—as it has been characterized —'far-fetched'. The operation of selective forces in statistical investigations can be a very subtle process, and no factual studies have been made to answer the question of their possible importance for the present situation. Opinions expressed of their irrelevancy appear to be based wholly on conjecture.*

Nor is it conclusive that the considerable number of statistical studies that have been published[2, 3] all agree in showing an association between smoking and cancer of the lungs. On the contrary, undeviating consistency of statistical results all in support of the same conclusion is in some circumstances the hallmark of spurious statistical correlation. If correlation is produced by some elements of the statistical procedure itself, it is almost inevitable that the correlation will appear whenever the statistical procedure is used. It was notable at the time of issue of Pearl's report showing a negative correlation between tuberculosis and cancer, previously referred to, that the negative correlation was shown without exception, not only in the data as a whole, but in each sub-grouping by race, sex and age.† The question naturally posed itself: If the antagonism between tuberculosis and cancer is so consistently and strongly operative that it is obvious whenever statistical data are assembled for examination, even admittedly imperfect data, which is the corresponding pathologic process not evident in individual cases? I confess that I entertain similar misgivings with respect to the significance of the uniformly consistent statistical results showing an association between smoking and cancer, so out of line with lack of parallel biologic findings in individuals. I shall return to this point later.

ANCILLARY EVIDENCE

The investigations under consideration had their origin in an idea that there is an association between smoking and cancer of the lungs; and although now a possible relationship of smoking to coronary heart disease and even to other diseases is being broached, the relation to lung cancer is still generally the one of central current interest. In the hypothetical development of the origin of the selective association described above, specific diseases are not involved except so far as some causes of death will, more than others, have prodromal symptoms that have some particular reference to the investigation in hand, and so can be the basis for the selection into or out of the experimental population.* It is pertinent therefore to examine the data of the American Cancer Society study, as regards the relation of smoking history to deaths from other diseases than lung cancer. In table 5 is shown a comparison, between the cigarette smokers and non-smokers of cigarettes, of death rates from all causes and from various specific causes. An examination of the table shows that the death rates, not only from cancer of the lungs but also from cancer other than cancer of the lungs and from coronary heart disease, are greater among the smokers than among the non-smokers of cigarettes.† Perhaps more interesting, however, is the fact that the death rates from causes other than either cancer (of any organ) or coronary heart disease are also higher for the cigarette smokers than for the non-smokers of cigarettes.‡ In short, so far as the published data

* The analytical statistical problem dealt with can be considered as an aspect of the general problem of 'competitive risks' as formulated by Fix and Neyman[13] and by Neyman.[14] The mathematics of the problem seems to have received little attention; indeed even the existence of the problem is not widely appreciated.

†The finding itself was later corroborated by other workers[15] but with a different interpretation.

* Deaths from accidents, for instance, could not artificially appear to be related to smoking by way of the selective mechanism which I described, since one could not have a present selection on the basis of an unknown occurrence of the future.

† A comparison with respect to death rates from cancer other than lung cancer, and for coronary heart disease is given by Hammond and Horn. The death rates from causes other than cancer or coronary heart disease were computed from data in their publication.

‡ This fact, as well as some other statistics given in the present paper, has already been noted by Arkin.[16] The present analysis, however, was completed before the appearance of his publication and anything in common between them has been arrived at independently.

TABLE V: DEATH RATES, CIGARETTE SMOKERS AND NON-SMOKERS, SPECIFIC DISEASES, AMERICAN CANCER SOCIETY STUDY*

Age Years	Death Rate, per 100,000 per Year									
	All Diseases		Cancer, Lungs		Other Cancer		Coronary Diseases		Other Diseases	
	Cigarette Smokers		Cigarette Smokers		Cigarette Smokers		Cigarette Smokers		Cigarette Smokers	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
50–54	602	955	6	46	91	103	230	442	274	365
55–59	1,072	1,523	19	89	158	192	440	727	454	515
60–64	1,444	2,375	6	103	225	367	592	1,095	622	811
65–69	2,662	3,259	45	127	358	502	1,115	1,439	1,144	1,191

* Twenty months' exposure (median) assumed for all individuals in the American Cancer Society study. The rates for cancer of the lungs and for "other diseases" were calculated from figures given in the publication of the study.[10]

of the American Cancer Society study make it possible to tabulate death rates by specific diseases, it appears that the death rates from each specific disease are higher among the cigarette smokers than among the non-smokers of cigarettes.

Do then the statistics of the American Cancer Society study support the hypothesis that cigarette smoking causes cancer of the lungs? In one sense they do, since the age-specific death rates from cancer of the lungs for the cigarette smokers in the population are higher than the death rates from cancer of the lungs among the non-smokers of cigarettes. In another sense, the results do not corroborate this specific idea, for they prove too much. If the finding of a higher death rate from cancer of the lungs among smokers in the population studied is proof that smoking causes cancer of the lungs, the finding that the death rate is higher for cancer other than cancer of the lungs is proof that smoking causes other cancer too. And since the death rate is higher for coronary heart disease, smoking causes coronary heart disease; and since it is higher for all other specific diseases for which the statistics have been studied, smoking causes some or all of these diseases. It does not seem unfair to say that, so far as the American Cancer Society study is concerned, the hypothesis of causation of cancer of the lungs by smoking stands or falls with the conclusion that smoking causes also other cancer and also coronary heart disease and also other diseases than either cancer or coronary heart disease. Indeed the question raised by the findings in the American Cancer Society study of higher death rates among cigarette smokers is not, 'Does cigarette smoking cause cancer of the lungs?' so much as it is, 'What disease does cigarette smoking not cause?'

The association of cigarette smoking of deaths from other diseases than lung cancer is shown in the American Cancer Society study, not only in the finding at all specific ages of a higher death rate from these other diseases for smokers than for non-smokers, but also in a positive correlation between the death rate and the *amount* of smoking. In table 6 is shown the death rate from 'other causes', for the group 'never smoked' and for each of the three classes of amount of current

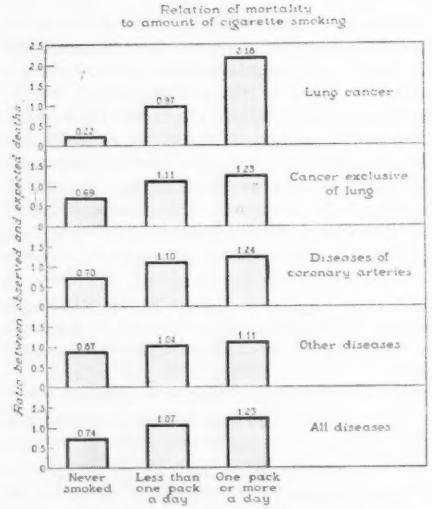
TABLE VI: DEATH RATES, OTHER CAUSES THAN CANCER OR CORONARY HEART DISEASE, IN RELATION TO AMOUNT OF CURRENT CIGARETTE SMOKING, AMERICAN CANCER SOCIETY STUDY*

Cigarette Smoking	Death Rate, per 100,000 per Year			
	Age, Years			
	50–54	55–59	60–64	65–69
Never smoked ..	295	460	586	1,078
Less than ½ pack a day	353	434	920	1,223
½ to 1 pack a day ..	368	498	812	1,310
1 pack or more a day	372	613	865	889

* Twenty months' exposure (median) assumed for all individuals. The calculations of the death rates in this table are based on the individuals who reported themselves as current cigarette smokers, and those who reported themselves as never having smoked, as are the similar calculations in the publication of Hammond and Horn. The rates for the group "Never smoked" are not the same as those given in table IV and table V for non-cigarette smokers, because the last include smokers of cigars or pipes or both.

cigarette smoking recorded in the American Cancer Society study, for each 5-year age class of the data. It will be seen by examination of the details of the table that the death rate increases steadily with increase of amount of smoking, in each age group, with a few exceptions that reasonably may be attributed to sampling fluctuation.

The increase of death rates with increase of amount of reported cigarette smoking may be exhibited clearly by use of the index employed by Doll and Hill,[9] consisting of the ratio of the total observed to expected deaths, for each class of amount of smoking. These are shown in the figure. It may be seen that the deaths from cancer of other sites than the lungs, from diseases of the coronary arteries and from 'other diseases', as well as deaths from lung cancer, all show a continuous rise of death rate with increase of amount of smoking.



Increase of mortality with increase of amount of current cigarette smoking in data of the American Cancer Society study.[10] Mortality measured in terms of ratio between observed and expected deaths. (Method of Doll and Hill.)[9] Amount of smoking in three groupings; the amounts measured as 'less than ½ pack a day' and '½ to 1 pack a day' have been combined because of a curious reversal of regression in the original data as respects these two amounts, in the case of deaths from cancer. (The regularity of the reversal in the specific age groups and the fact that it occurs only with the cancer deaths suggest a clerical transposition.)

A positive regression of mortality with amount of smoking is shown for all specific disease groups including other diseases than cancer or coronary heart disease.

Doll and Hill[9] reasonably considered the finding of association between death rate and *amount* of smoking to be the strongest evidence of a real association, and from general intuitive considerations this would appear to be cogent. The appearance in the American Cancer Society study of a positive correlation between amount of cigarette smoking and death rate from causes other than lung cancer, including deaths from cancer of other sites, coronary heart disease and other diseases, would from such considerations be considered cogent statistical demonstration of a meaningful, even causal, association between smoking and death from these other causes. Perhaps this is what it does mean. But if one is unwilling to believe that smoking can be so minutely definitive a determinant of death that it affects differentially even deaths from causes other than cancer or coronary heart disease, according to whether there is a questionnaire report of smoking of 'less than one-half pack a day', 'one-half to one pack a day' or of 'more than one pack a day', then the finding can perhaps be regarded as evidence that spurious association can be produced in statistical data collected under other than strictly experimental conditions, perhaps by way of the mechanism of competitive selection rates as described above, perhaps by some other mechanism.

CIGARETTE SMOKERS IN COMPARISON WITH UNITED STATES WHITE MALES

It has been noted that the level of the age-specific death rates of the population of the American Cancer Society study, for the total population and also for non-smokers of cigarettes, is lower than those for United States white males. Those comparisons were made in connexion with the consideration of the selective character of the data. Another point is considered if we compare the death rates of the cigarette smokers in the American Cancer Society study with those of United States white males. These are shown in table 7. Here it is seen that as repects deaths from all causes the age-specific death rates, even for the cigarette smokers, are lower than those for United States white males. This relation in fact holds without exception also for deaths from cancer of other sites than the lungs, and for deaths from other diseases than cancer or coronary disease. Even as respects deaths from cancer of the lungs the age-specific death rates of the cigarette smokers are practically equal to those for United States white males. Only

TABLE VII: DEATH RATES, CIGARETTE SMOKERS OF THE AMERICAN CANCER SOCIETY STUDY AND UNITED STATES WHITE MALES*

Age, Years	Death Rate, per 100,000 per Year									
	All Diseases		Cancer, Lungs		Other Cancer		Coronary Diseases		Other Diseases	
	A.C.S. Cigarette Smokers	U.S. White Males	A.C.S. Cigarette Smokers	U.S. White Males	A.C.S. Cigarette Smokers	U.S. White Males	A.C.S. Cigarette Smokers	U.S. White Males	A.C.S. Cigarette Smokers	U.S. White Males
50–54.. ..	955	1,206	46	50	103	148	442	426	365	582
55–59.. ..	1,523	1,891	89	85	192	259	727	701	515	846
60–64.. ..	2,375	2,793	103	114	367	406	1,095	1,018	811	1,255
65–69.. ..	3,259	4,089	127	127	502	609	1,439	1,438	1,191	1,915

* Rates in this table calculated in the same way as for table IV.

as respects deaths from coronary heart disease are the death rates of cigarette smokers consistently higher than those of United States white males. It is notable, and perhaps significant, that if we take for comparison of the death rates of the cigarette smokers, not the non-smokers of cigarettes in the sample of the American Cancer Society study, but the comparable general United States population, the only specific disease that shows death rates consistently unfavourable to cigarette smoking is coronary heart disease, and this is the particular disease group for which there is independent biologic evidence that cigarette smoking may be deleterious. For each of the specific diseases except coronary heart disease, the cigarette smokers of the American Cancer Society study show equal or more favourable rates than the comparable United States white male population. It suggests itself that perhaps the general United States population is a better 'control' group with which to compare the death rates of the smokers than is the sampled population of non-smokers of cigarettes in the American Cancer Society study, the death rates of which are so extraordinarily low as to allow little doubt that it is very highly selected.

It has been suggested, on the basis of the findings in the publication of Hammond and Horn, that an active educational campaign be conducted to warn the American public that cigarette smoking exposes them to an increased hazard of developing cancer. Such a proposal seems poorly founded when an examination of the data on which the conclusions of the study rest discloses that the cigarette smokers in the American Cancer Society study are enjoying equal or lower death rates from cancer than the general public is experiencing, and that their over-all death rate is also lower. Calculations which have been made of the number of lives which could be saved in a year if all men stopped smoking cigarettes are based on the fallacious practice of applying the difference between the death rates of strata observed in the population of the American Cancer Society study to the United States population, the general death rates of which are materially different. It would seem more cautious, not to say more logical, to assume that whatever selective forces were responsible for the difference evident between the death rates of the investigated population taken as a whole and the United States population, affect also the *difference* of death rates between selected strata of the population. Why should a complex mechanism of selection which effects a falsification in representing the incidence of deaths in each of two groups concerned in an investigation act in a way so co-operative with the objectives of the investigating statistician as to render the *difference* between the false death rates a correct reflection of the difference between the true death rates? An examination of the history of science would hardly disclose nature to be so helpful in balancing out the errors of observational data.

BIOLOGICAL CONSIDERATIONS

A disquieting element in the array of observations which have been assembled pointing the finger of accusation at smoking as a cause of lung cancer is that it is so ample, yet it is so exclusively statistical. There are lacking observations of the pathologic process of which the statistics are only the supposed reflection. If smoking causes cancer in many individuals, it does so in each one of these individuals separately and by way of some material physico-biologic process. One would

expect a body of clinical and pathologic observations to have accumulated over the years suggestive of such a process. The notable lack of these, taken together with the abundance of statistics, should, in view of previous similar experience, arouse suspicion that we may be dealing with a purely statistical phenomenon related to the way the statistics were obtained.

If cigarette smoking is so effective in causing lung cancer that one can see its evidence statistically so impressively in so short a time as 20 months as it is on view in the report of Hammond and Horn, then we can reason that it is a very potent cause. Why then cannot lung cancer easily be produced experimentally? If, to counter this question, it is argued, as it has been argued, that the cancer produced in the short period of observation is the result of a cumulative effect of many years of exposure to smoking, then one wonders why pathologists have not reported, from the enormous number of necropsies with careful tissue examination which have been performed over the years, evidence of a profound chronic process which retrospectively could be allocated as the precursor of smoking-produced cancer.* Since the American Cancer Society study shows cancer other than lung cancer to be associated with smoking, it is not only in the lung but in all cancer-susceptible tissues that such changes should be found. It is of course possible further to argue that the widespread cellular damage by smoking that is going on for years, is of a fundamental biochemical nature not visible to the pathologist and not yet discovered by the chemist, and that animal experiments are futile because humans are the only animals susceptible to smoking-produced cancer. But such explanations are hardly more than a restatement of the paucity of direct evidence. Moreover, even if the process of causation of cancer by smoking is 'on the average' very long, say many years, still we should expect on the basis of observations of other biologic characters, that the period of incubation would be variable and that at least in a small proportion of cases it would be very short. Why then over the years have we not seen individual case reports of the appearance of fulminant cancer in association with acute exposure to smoking? I mention these few isolated questions merely to illustrate the general fact that clinical experience with individual patients has not produced independently an impression that cancer in patients is associated with smoking. If one can imagine all the statistical evidence, including that from vital-statistics reports, not to have appeared, then I believe that there is nothing substantial in the record of clinical or pathologic observations on individuals that would have suggested smoking to be the cause of cancer. In these circumstances it seems premature to conclude definitely that it is the cause.

Actually the American Cancer Society study does not point specifically to association of smoking and cancer, for all specific diseases for which the number of cases permits examination show association, exhibiting a larger death rate among smokers than among non-smokers. Therefore, if the association found is not statistically spurious and is to be explained as a biologically causative effect, it is not on these findings specifically a carcinogenic effect but something which influences broadly whatever may increase the susceptibility of the organism to fatal disease. Now, the most important known 'cause' of cancer and some other diseases, notably those of the cardiovascular system, is *age*. We might say speculatively that smoking accelerates the rate of living and advances age and age causes cancer. The supposed effect of smoking, if it exists, may be to stimulate those trophic processes, of which little is known, that constitute the biology of ageing. The idea is not entirely implausible or without support in existing literature. It is in keeping with Pearl's idea that duration of life is inversely related to the *rate of living*[17] and with Pearl's own study of the effect of heavy smoking on longevity.[18]

WANTED—AN ADEQUATE PROGRAMME OF EXPERIMENTAL VERIFICATION

In most recent reviews of the statistics on smoking and cancer, the studies referred to have been divided into two types which have been designated respectively as 'retrospective' and 'prospective'. This distinction is made, I presume, having in mind the development of cancer. In the retrospective studies, when the investigation begins, the cases with cancer are already developed and designated, while in the prospective type the cases with cancer are still to be assigned. In the retrospective studies the cases are primarily differentiated as to cancer and secondarily

* Since this writing there has come to my attention some unpublished work by Auerbach and also by Ryan and McDonald, presenting observations on epithelial changes in the larynx and lung that are of interest in this connection.

investigated as to smoking; in the prospective studies the cases are primarily differentiated as to smoking and secondarily investigated as to the development of cancer. The retrospective type of study generally has been recognized to contain certain particular difficulties for inference, of which the prospective type is free. I do not doubt that the prospective type of study does mitigate some important objections which have been raised against the retrospective type of study. In a crucially important sense, however, both of these types of study are retrospective. If in the prospective type of study—exemplified in those of Doll and Hill[9] and of Hammond and Horn—the designation of the cases with and without cancer is 'prospective', the designation of each individual as to whether he is a smoker or a non-smoker is not prospective, for this is already accomplished at the initiation of the study. It is just this which opens the way to 'selection'.

The type of study which is genuinely prospective is the experimental study, for here one begins with neither variable predetermined, but instead with the entire group of individuals undifferentiated in respect of either of the two variables, the association of which is under investigation. Separation of individuals is then made in respect of one variable—the putatively 'causal' variable—*at the will of the experimenter,* and according to well-defined statistical principles of randomization. The procedure is described in detail with great acumen by Hill[19] for the study of association of therapeutic effect and the administration of specified drugs. The great care of the planned systematized randomization employed in such investigations involves considerable, sometimes very formidable, practical difficulties, and it would hardly be insisted on if it were not essential for a valid statistical inference of association implying causation of therapeutic effect. If, in the prospective studies on the association between smoking and the development of cancer of the lungs, randomization has not been employed as respects the smoking variable, it is not because randomization is less necessary here than in clinical trials for the critical evaluation of the scientific significance of the results, but only because of the practical difficulties involved. It seems at the moment quite outside the realm of practicality to perform an experiment in which persons randomly designated are subjected to various degrees of smoking, with prospective observation on the development of cancer.

But in science there is no substitute for experiments. It is a central purpose of this essay to urge that an adequate programme of experimentation with animals be accomplished, before definitive conclusions are drawn regarding the association between smoking and cancer. What is to be considered an adequate programme of experiments will bear much thinking about, and by persons more competent and more experienced than I am as regards the technical aspects of the problem, but what I have in mind as a minimum is a forthright *ad hoc* check on the prospective investigations of Doll and Hill, and of Hammond and Horn. It is notable that these investigations, which have provided affirmative evidence, involved large numbers of individuals, and that they were pursued with the methods of statistical epidemiology. If they are to be verified experimentally it suggests itself that a similar procedure should be employed applied to animal populations. I refer specifically to 'inhalation' experiments biologically simulating the exposure of the respiratory system to cigarette smoking in different intensities, which is represented in the prospective studies referred to as different amounts of cigarette smoking and resulting—it has been inferred from these studies—in the production of correspondingly greater frequencies of cancer.

The variety or varieties of animal to be used is one of the questions on which counsel will be wanted from specialists, but since mice are known to develop cancer of the lung as well as cancer of other sites[20] and some small-scale experiments with these animals show promise of significant results,* I should think mice should be satisfactory experimental animals. Careful statistical control should, of course, be exercised, with an adequate number of animals used with each of several intensities of smoking exposure, stratified possibly on some pertinent biological variables such as age and weight. Time of death with pathologic findings at necropsy would be the dependent

* For instance, in a report by Campbell[21] 74 mice exposed to diluted cigarette smoke and tarry matter were compared with 76 control mice. For the exposed mice the mean duration of life was 417 days and 24% were found with primary lung tumours, while for the controls the mean duration of life was 427 days and 14 per cent developed primary lung tumours. The number of animals used is small and details respecting the pathologic character of the tumours are wanting, but the general results of the experiment are corroboratory of the thesis that cigarette smoking decreases longevity and increases the incidence of lung cancer.

variables which, subjected to life-table analysis, could summarize the results.

An experimental programme of appropriate dimensions doubtless is not something to be undertaken out of hand, but neither is it anything that can be considered prohibitively difficult. As I have explained previously, I do not believe that from the statistical studies so far accomplished one can conclude definitively that smoking causes cancer, or even that necessarily it is 'associated' with it. On the other hand, at the very least these studies pose a strong presumption that smoking *may* cause cancer and/or *may* otherwise be deleterious to health and longevity. Considering that we may have here a clue to the etiology of human cancer and in view of the social importance of even the belief that it causes cancer, something more seems in order than sporadic efforts on the part of isolated individuals who happen to be particularly interested, but who are not necessarily adequately equipped with the required laboratory facilities or even by themselves with all the technical knowledge required for a comprehensive experiment. Aside from the direct interest of such an experiment in relation to the interpretation of the statistical studies under discussion, the opportunity to perform a study in experimental epidemiology involving possibly an environmental factor affecting the 'rate of living', possibly an etiologic agent of cancer, seems unusual in its potentiality for elucidating a basic problem in human ecology.

In reviewing the present paper before it was dispatched to the printers, I realized that I may have over-elaborated some of the points and produced an unbalanced impression. I do not fail to appreciate the great pioneering effort which the statistical studies on smoking and cancer represent. It was not intended to denigrate them, so far as they are considered tentative evidence that there is some relation between the two. My thesis is only that it is unwarranted to conclude from them that a meaningful association already has been proved beyond doubt, as some writers have asserted and as appears to be widely accepted in the United States.[10, 16] Much less do I believe that causation has been established. I think that the possibility that selection is the source of the observed association has not been given sufficient weight, and that much more work must be done, and time allowed for its evaluation, before a responsible definite opinion can be had as to the precise significance of the findings.

APPENDIX NOTE 1. OTHER STUDIES THAN THAT OF THE AMERICAN CANCER SOCIETY

It has been mentioned in the text that the study from the American Cancer Society was taken as the basis for the present analysis because it is the prospective study which is most amply provided with detailed data, of any published up to the time of the present writing. The conclusion I have drawn from consideration of that study is that, since the sample was not obtained by appropriate methods of randomization, it is possible that a selected sample was obtained in which association between smoking and deaths from lung cancer has been produced by the interaction of competing selective risks as described or by some other selective mechanism. The detailed data of the American Cancer Society study contain evidence supporting the hypothesis that that is what may have happened. How do other reports which have appeared come out when they are inspected with these considerations in mind? The study most directly to the point is the prospective study of Doll and Hill,[9] which antedated that of the American Cancer Society and which, together with the retrospective study of the same authors,[22, 23] is in many ways more carefully and critically analyzed by the authors than is the study of Hammond and Horn. The question to be considered is 'Does evidence appear of selection on the pertinent variables, smoking or death or both?'

1. General Measure of Selection. The questionnaire inquiring about smoking history[6] . . . 'was sent on October 31, 1951, to 59,600 men and women on the *Medical Register*. Of the 41,024 replies received, 40,564 were sufficiently complete to be utilized'.[9] Thus the usable records referred to 68% of the population designated for study. The present (preliminary) report of Doll and Hill concerns itself only with 24,389 men aged 35 years and above, who answered the questionnaire, and it is possible that this sub-group represents a different proportion of the original population. But the percentage of 32, representing the fraction of the population in which association was to be studied, that failed to enter the investigation provides a measure of the potential of selection present in the study.

2. Selection on Deaths. Doll and Hill found that the smokers in the sampled population experienced higher death rates from lung cancer than did the non-smokers. But so far as the level of death rates for the total sampled population is concerned, the authors

recognize that there has been selection favouring lower death rates among the doctors, and offer an explanation of how this has come about. They say:

'Why should the rates for the doctors be so much lower? One important reason . . . is, we believe, that doctors who were already ill of a disease likely to prove fatal within a short space of time would have been disinclined, or indeed unable, to answer our inquiries. In other words, we should learn of their deaths, but we would have no corresponding completed questionary on our files. That this may well be true is shown (*a*) by the relatively low death rate from all causes that we have recorded —namely, 14.0 per 1,000 per annum, against 24.6 per 1,000 for men of all social classes in the same age group in the U.K. in 1951, . . .'

So far as deaths from specific diseases are concerned, a comparison is made by Doll and Hill[9] with respect to deaths from cancer of the lungs among men aged 45 through 74 years as experienced in the prospective study and as estimated from their retrospective study among residents in Greater London in 1950. The standardized death rate per 1,000 men from cancer of the lungs for physicians in the prospective study was 0.73; for the residents of Greater London it was estimated as 1.97. So far as the latter can be taken as representative, the death rate from cancer of the lungs, as well as the total death rate, in the sampled population is smaller than that of the comparable general population. Indeed, even among the heavy smokers (25 gm. + per day) the total death rate 16.3, and the death rate from lung cancer, 1.45, are smaller than the respective rates for the general population. Thus it is seen that, as is the case with the sampled population of the American Cancer Society study, the sampled population of the prospective study of Doll and Hill has been subjected to severe selection in favour of low death rates.

3. The Smoking Variable. The prospective study of Doll and Hill[9] shows 87.3% of smokers of all forms of tobacco and 72.7% of cigarette smokers among the physicians in the sampled population. The corresponding percentages shown in their retrospective study[23] in the control population of patients without lung cancer are considerably higher, being respectively 95.5 and 89.0. Part of the difference shown may be due to differences as to social class, age and sex between the populations, as well as to differences in definition of smokers used in the different studies. However, it is characteristic of the studies published on the association between smoking and cancer that the percentage of smokers indicated in the controls varies over a wide range. Among 14 retrospective studies reviewed by Cutler,[2] the percentage of smokers among the controls varies from 69 to 95. It appears that whether or not an individual is recorded as a smoker in these studies depends on the circumstances of the study. It is not unreasonable to suggest that whether an individual records himself on a questionnaire as a smoker also is dependent on circumstances, and I do not see how one can be sure that this is independent of the general health of the individual or of the appearance of the presence of a disease which, it is known to the recorder, is under investigation. Specifically, however, I do not find evidence of selection as respects smoking in the prospective study of Doll and Hill. On the contrary, in their retrospective study[23] these authors quote the results of a social survey of Greater London which shows 87.9% smokers, which, while it is low in comparison with the 95.5% smokers shown among the controls of that retrospective study, agrees well with the 87.3% shown in the prospective study. It has been suggested that the prospective studies provide an opportuntiy to validate the questionnaire reports of smoking habits, if in the case of each individual deceased, a 'retrospective' inquiry is made. There is need to get some light on why the percentages of smokers reported among the controls in the retrospective studies are so different from those reported in the prospective studies.

4. Other Diseases than Lung Cancer. In the analysis of the data provided in the publication of Hammond and Horn it was found that the smokers in the population died at higher rates than the non-smokers, not only from lung cancer, but also from other cancer, from coronary heart disease and from diseases other than any of these. The prospective study of Doll and Hill agrees in showing an association of smoking and death from lung cancer and from coronary heart disease, but no association is found with deaths from cancer other than lung cancer, respiratory diseases other than lung cancer, cardiovascular disease other than coronary heart disease or diseases other than any of these diseases. This result is more in keeping with the hypothesis of a specific action of smoking in causation of disease, and it may be that selective association exists in the sampled population of the American Cancer Society and not in the sampled population of the prospective study of Doll and Hill. Nevertheless the material differences between the study of Hammond and Horn and that of Doll and Hill as regards

association between smoking and diseases other than lung cancer and coronary heart disease, unless one is to believe that smoking affects very differently American males generally than English male physicians specifically, demonstrate that the appearance of association between smoking and disease, in statistical studies, can be influenced by the circumstances in which the sample is taken.

APPENDIX NOTE 2. CHECK ON SELECTION HYPOTHESIS

Evidence on whether or not the association shown in the prospective studies of Doll and Hill[9] and of Hammond and Horn has been produced spuriously by selection will perhaps be provided in the projected study on the records of the Veterans' Administration. If this study will deal with a predesignated cohort of veterans, if these are traced completely or practically completely, if the results show the death rates for the group as a whole to be fairly comparable with the rates for United States males of the same age distribution, if the percentage of cigarette smokers agrees fairly well with general statistics as shown by independent studies of cigarette smoking, and if association between cigarette smoking and death rate from cancer is found, then this will provide evidence that the source of the observed association in the present studies is not a selective mechanism of the kind I formulate.*

Perhaps useful relevant information can be obtained also if a subsidiary detailed study is made on the records of the study of Doll and Hill[9] in respect of those physicians on the registry who did not fill in the questionnaire addressed to them regarding their smoking history. What was the death rate of these compared with those who did? Could something in the way of a special investigation be made on a sample of these cases to ascertain the percentage of smokers among them to be compared with the percentage found for the physicians included in the study?

A check will be available when prospective studies have been continued long enough. Experience of insurance companies indicates that selection effected by initial medical examination, and by self-selection is 'worn off' in about 3 to 5 years.[24] After about that time we may expect that the age-specific death rates of the sampled population as a whole should approximate those of the general comparable population. If after, say, 5 years have elapsed since the beginning of the study, comparison is made of the death rates of smokers and non-smokers over a 2-year period, referring only to the individuals who have survived 3 years, and the differences between smokers and non-smokers are found to be just as large as earlier, it will be reasonable to conclude that the importance of selection in the sense discussed in the text is negligible. In this connexion I hope it is not amiss to suggest that when sufficient data will have been accumulated in the prospective studies, the results will be presented in the form of a life-table analysis. At present in the prospective studies[9, 10] the death rates are computed by dividing observed deaths by total number of corresponding individuals entered in the population. While it is not to be supposed that there is any important difference in exposure times of the smoking and non-smoking groups compared, it would seem preferable to use an analysis that takes account of period of exposure,[25, 26] and which at the same time presents the annual death rates in a way in which they are immediately seen in relation to time of entry into the investigation.

* It is to be hoped that all the necessary effort will be made in this investigation to secure a complete follow-up. Otherwise, even if its findings should be similar to those of other prospective studies, a cloud of doubt will hang over it because of the possible effects of selection. It is desirable also that some validation of the smoking questionnaire be attempted, and at least for a sub-sample some data be obtained on the relative socio-economic characteristics of the populations which are compared, as suggested by Arkin.[16]

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REVIEWS OF BOOKS

COLLAGEN DISEASES

Collagen Diseases. By John H. Talbott, M.D. and R. Moleres Ferrandis, M.D. (Pp. 225 + Index. With 30 Figs. and 16 colour plates. $6.50.) 1956. New York and London: Grune & Stratton, Inc.

In recent years, certain diseases (collectively known as 'collagen diseases') have been more widely recognized and more frequently diagnosed than before. There probably has been an increased incidence of these conditions and most practitioners encounter many such cases during their careers. However, some diseases in this group are rare, but figure prominently in current medical literature. Among these less common conditions are systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma and thrombotic thrombocytopenic purpura, which are dealt with in this publication.

In their monograph the authors have briefly discussed the incidence, etiology, pathology, clinical and laboratory findings, diagnosis, clinical course and treatment of these conditions. They have also presented information about the historical aspects of these diseases and their relationship to one another. The conciseness of the treatises enables the reader to obtain a good overall picture of the situation. Hence this book may be of great use to the student and to those practitioners whose knowledge of these conditions is limited.

It is not intended as a reference book, but for the reader who wishes to obtain more detailed information about the diseases concerned, there is an extensive and reasonably up-to-date bibliography with 540 references.

The book is well illustrated with 15 colour plates and 30 black-and-white photographs. Its style allows easy comprehension of difficult subjects. It is to be warmly commended to under-graduate and post-graduate students and to practising doctors.

NEURO-OTOLOGY

British Medical Bulletin: Neuro-Otology. Vol. 12, No. 2. (15s. per single copy, £2 per volume of 3 numbers, with Index). 1956. Publishers: Medical Department, The British Council, 65 Davies Street, London, W.1, England.

This new number of *British Medical Bulletin* fills a gap in the literature of the subject of Neuro-Otology.

Planned under the chairmanship of Dr. E. A. Carmichael, it shows the active state of otological research and the successful results achieved during the past 25 years. The papers in this number, by physiologists, physicists, pathologists, surgeons, clinical investigators, histologists and biochemists, collected together under the scientific editorship of Dr. C. S. Hallpike, reveal how each of these separate branches of science has contributed to the development of this complicated study of the neurophysiology of the ear.

Sir Bryan Matthews, in his introduction to the number, writes:

'The stimulus to research in this field by the formation in 1944 by the Medical Research Council of their Otological Research Unit, and the very active interest taken by the Medical Research Council in the otological health and hazards of the nation, have played an important part in the great advances achieved and in keeping Great Britain in the forefront of research in this field.'

CORRESPONDENCE

MEGIMIDE AND DAPTAZOLE: A NEWER METHOD OF TREATMENT OF BARBITURATE COMA

To the Editor: Of the various methods of attempting suicide, by far the commonest is the ingestion of barbiturates. Hardly a week elapses in which a case of barbiturate intoxication is not seen in the medical wards of the General Hospital, Johannesburg. Fortunately, the majority of cases do not give rise to any undue anxiety in that when seen they are in the 'stuporose state'.

A few, however, are admitted in deep coma. It is in this type of case that treatment in the past has not given any gratifying results. The methods available such as picrotoxin, Coramine, lumbar puncture (so-called dry tap), have not been of great assistance in the deeply comatose case. The method of countering barbiturate intoxication as described by Shulman, Shaw, Cass and Whyte (Brit. Med. J., 21 May 1955) prompted us to try this procedure in our cases.

Case Report: Mr. H. L., aged 38, was admitted to a medical ward on 11 April 1956 at 8.30 p.m. in a deeply comatose state. He had last been seen at 8 p.m. on 10 April 1956. He had been found by a friend, on the morning of admission, unconscious in bed. His wife informed us that the patient had been taking sleeping 'capsules', especially over the last few weeks. He had had a previous admission to hospital in September 1954 because of fainting attacks. His previous notes suggest that no basis for these attacks was found and that he was diagnosed as 'hysteria'. The patient signed himself out of hospital some 5 days after admission.

On this admission it was difficult to assess the amount of barbiturate (presumed to be Seconal) and the time at which the drug was taken.

On Examination: The patient was deeply comatose. Respirations were shallow and the rate 20 per minute. Cyanosis of the mucous membranes and the extremities was present. Blood pressure: 100/70 mm. Hg. Pulse rate, 84 per minute: regular and weak. All reflexes (including the corneal reflex) were absent. The pupils were normal in size and shape and reacted sluggishly to light.

The heart sounds were faint but evidence of aortic and mitral valvular lesions was present.

Treatment: A 5% glucose-saline intravenous drip was commenced at 8.50 a.m. One c.c. of Daptazole followed immediately by 10 c.c. of Megimide was injected into the tubing. This procedure was repeated every 3-5 minutes for the next hour. After about half an hour, during which time 7 c.c. of Daptazole and 70 c.c. of Megimide were given, the patient's corneal reflex became positive, respiration became deeper and the cyanosis cleared. During the next half hour another 6 c.c. of Daptazole and 60 c.c. Megimide were given. At the end of an hour the patient commenced to groan and moved about in bed. At this stage his reflexes were present and equal throughout. Eye movements and lachrymation were obvious. The pupils reacted briskly to light. The patient was considered to be in the 'safe' stage and no further therapy (besides Penicillin 500,000 units 6-hourly) was given. Some 5 hours later the patient was restless and groaning. The following morning he was conscious and, after having had a good breakfast, asked to be allowed to sit in a chair. He was discharged 4 days after admission.

Discussion: Daptazole is a non-specific respiratory stimulant, but has also a mild antagonistic effect against the barbiturate, while it also enhances the action of Megimide. Megimide is a barbiturate antagonist.

During the treatment of patients with these new substances no attempt should be made to waken the patients. The injections are repeated until the patient is brought to a 'safe' state, i.e. the return of muscle tone reflexes. At this stage the patient shows evidence of voluntary movement.

During the course of treatment, preferably after each injection, a note should be made of blood pressure, reflexes, eye movements, pupil response, etc. Toxic effects, according to Shulman *et al.* (Brit. Med. J., 21 May 1955) are uncommon. Occasionally vomiting and slight twitching of the fingers may occur. An interesting point, according to Shulman *et al.*, is that since Megimide has some analgesic effect, supraorbital pressure used as a means to determine improvement, may not be reliable.

Daptazole is unstable and is prepared by adding 20 c.c. of normal saline to each vial. Such a solution contains 15 mg. of Daptazole per c.c. Megimide is in solution and contains 5 mg. per c.c. Since Daptazole is unstable it should be used within 12 hours of preparation.

V. BOTOULAS, M.B., B.Ch.
C. CURLEWIS, M.B., B.Ch.
J. BECK, M.B., B.Ch.

Johannesburg.

PREVENTION OF MATERNAL AND FOETAL MORTALITY AND MORBIDITY

To the Editor: A striking feature of hospital obstetrics in certain areas of South Africa is the unnecessary maternal and foetal mortality and morbidity due to delay in reporting significant signs and symptoms.

I have arranged pamphlets (which I hope to have adopted locally) to cover these points in simple English, Afrikaans and Xosa. These can be obtained from me on request.

I would like to acknowledge the help given by Dr. Ware and Dr. McLean (the Superintendents of Livingstone and Provincial Hospitals) and their secretaries Mrs. Brann and Mrs. Glover. Thanks for help in the translation go to Mr. Lanham (of Rhodes University), Dr. Steyn and Dr. Scholtz (of Livingstone Hospital), Dr. Fick (of the Provincial Hospital) and Dr. Molefe, Mr. Barley and Mr. Jeffrey Booi. I am also indebted to the medical and nursing staff for helpful criticism.

4 Western Road, JAMES MILLER,
Port Elizabeth. M.R.C.O.G.

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(J3/2H)

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Aansoeke moet gerig word aan die Registrateur, Universiteit van Pretoria en moet hom voor 15 September 1956 bereik.

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